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CONTENTS

Number 1, January

Editorial : Preface to the Publication of Japanese Heart Journal. *Hideo Ueda* . . i

Circulatory and Respiratory Changes Induced by Stimulation of the Thalamic Nuclei. *Hideo Ueda, Soichi Katayama, Hitoshi Goto, and Kiyoshi Ito* 1

The Study on Hepatic Blood Flow Determination by Au^{198} Colloid Using Deviced Recording Method.
I. New Apparatus for the Determination of Circulation.
II. Determination of Hepatic Blood Flow.
Masahiro Iio, Haruo Kameda, and Hideo Ueda 17

Studies on the Expired Alveolar Carbon Dioxide Tension in Chronic Pulmonary Emphysema with Special Reference to Pulmonary Arterial Hypertension. *Atsushi Sakamoto and Makoto Murao* 37

Effects of Insulin on the Electrocardiogram. *Saburo Mashima* 56

Respiratory Findings in the Neurocirculatory Asthenia. *Eiichi Kimura* . . . 72

Special Articles

Conceptional Changes of Electrocardiographic Theories as Developed by the Advent of the Microelectrode Technique. *Toyomi Sano* 81

Theoretical Consideration on Plasma Volume Determination. *Atsuo Nakanishi* 92

Case Reports

Congenital Aneurysm of the Right Coronary Sinus of Valsalva with Rupture into the Left Ventricle. *Sadataka Tasaka, Yawara Yoshitoshi, Kiyoshi Seki, Keizo Koide, Etsuro Ogata, and Kozo Nakamura* 106

Combination of Ventricular Septal Defect and Aortic Insufficiency—Report of Two Cases. *Iwao Ito, Goro Kaito, Tsuguya Sakamoto, Akira Nakajima, Tohru Kobayashi, Ryoga Ohmori, and Shigeaki Jogi* 113

Massive Occlusion of the Main Pulmonary Artery and Its Primary Branches with Subsequent Cor Pulmonale—A Case Report. *Sadataka Tasaka, Satoshi Ohta, Yamato Mishina, Hiroya Saheki, and Kiyoshi Machii* 120

Number 2, April

Editorial : Causes of Death in Japan with Special Reference to the Death of Cardiovascular Origin. *Hideo Ueda and Masaya Sugiura* 129

Cerebral Embolism in Cardiac Disease—The Clinical and Pathological Studies of 56 Cases. *Yutaka Takabatake, Hitoshi Goto, Kiyoshi Ito, Soichi Katayama, Toranosuke Hidaka, Akiyuki Yamada, Yoshio Ito, and Hideo Ueda* 135

Rheumatic Fever in Children—A Statistical Report in Japan. *Masahiko Okuni, Masahiro Oshima, Kazuo Okuyama, Yoshiaki Okamoto, Masao Iijima, and*

Yoshiro Obe 149

Studies on Myocardial Metabolism by Coronary Sinus Catheterization in Man —Relationship of Myocardial Metabolism to ECG and Cardiac Size. *Tachio Kobayashi, Yoshio Ito, Atsuo Nakanishi, Kazuzo Kato, Iwao Ito, Hiroshi Tsuyuki, Toshiyuki Atsumi, Akio Ota, Kenichi Harumi, Hisakazu Yasuda, and Mototsugu Watanabe* 157

The Influence of the Sympathetic Innervation on Carotid Sinus Activity. *Yoshiaki Masuyama* 169

Studies on the Vasomotoricity of the Cerebral Vessels. *Yoshizi Yamane, Jinkichi Ishiba, Hiroshi Fukaya, Akira Morisawa, Shigetaka Watanabe, Keizo Koide, and Kiyoshi Seki* 181

Synthesis and Pharmacology of Some Bis-quaternary Salts of the Bicyclo (2. 2. 2) octane Series, Including 2-(3-Dimethylaminoprophyl)-3 a, 4, 7, 7 a-tetrahydro-4,7-ethanoisoindoline Dimethiodide (KK-25-S)—A New Hypotensive Agent. *Ken'ichi Takeda, Keizo Kitahonoki, Tetsuo Mineshita, Ryonosuke Kido, and Tetsutaro Ikeda* 189

Electrocardiographic and Phonocardiographic Studies in Hypertension. Part I. Electrocardiographic Study with Special Reference to the P-Wave. *Tsuguya Sakamoto, Goro Kaito, and Hideo Ueda* 198

Electrocardiographic and Phonocardiographic Studies in Hypertension. Part II. Phonocardiographic Study with Special Reference to the Atrial Sound and "Q-1" Interval. *Tsuguya Sakamoto, Goro Kaito, and Hideo Ueda* . . . 213

The Quantitative Analysis of Vectorcardiograms of Normal Hearts and Left Ventricular Hypertrophy. *Toyomi Sano, Hisashi Ohshima, Hiromichi Tsuchihashi, and Takio Shimamoto* 226

Case Reports

A Case of Sinus of Valsalva—Right Ventricular Fistula Successfully Repaired by Surgery. *Takeshi Kuzuya, Hitoshi Tanabe, Hiroshi Kurihara, and Kizuku Kuramoto* 239

A Case of Idiopathic Cardiomegaly. *Tohru Kobayashi, Ryozo Okada, Tsuguya Sakamoto, and Satoru Murao* 248

Number 3, July

Editorial: Historical Review of Cardiology in Japan. *Hideo Ueda* 257

Studies on the Time of Valvular Movements in Mitral Valvular Disease with Ultrasonic Doppler Method. *Tsuneo Yoshida, Masayoshi Mori, Yasuharu Nimura, Shinpachi Takagishi, and Katsumi Nakanishi* 261

Experimental Studies upon the Reciprocal Rhythm. *Ichiro Dohi, Yutaka Dohi, Tsutomu Tada, Yahiro Mita, Ken Yoshida, Yasushi Matsuura, Riichi Maruyama, Shohji Koyama, and Torao Taketani* 275

Experimental Studies on the Nervous Control of the Renal Circulation—Effect of the Electrical Stimulation of the Diencephalon on the Renal Circulation. *Jugoro Takeuchi, Shigeru Yagi, Shosaku Nakayama, Takao Ikeda, Eiichi Uchida, Gosuke Inoue, Fujio Shintani, and Hideo Ueda* 288

Clinical Evaluation of KK-25-S—A New Ganglionic Blocking Agent. *Eiichi Kimura, Hiroshi Hannya, Kōji Yahata, and Kiyoto Satake* 300

Treatment of Hypertension with KK-25-S, a New Potent Ganglionic Blocking Agent. *Jugoro Takeuchi, Tadanao Takeda, Koji Nakajima, Takao Ikeda, Eiichi Uchida, Shigeru Yagi, Shosaku Nakayama, and Hideo Ueda* 308

Algebraic Reflections on the Vector Concept in Electrocardiography. Part I. Construction of the Electric Field. *Mitsumasa Sato* 317

Special Article: Reevaluation of the Solid Angle Approach in Electrocardiography Bearing on the Lead-Field Concept. *Tozomi Sano and Iwao Ogawa* . 325

Case Reports:

Bacterial Aortic Regurgitation with Musical and Associated Rumbling Diastolic Murmurs. *Hiroshi Watanabe, Tsuguya Sakamoto, Zen'ichiro Uozumi, Tohru Kobayashi, and Tadashi Sakurai* 333

A Case of Ebstein's Disease. *Kunio Matsuda, Toshio Ozawa, Hiroichi Niitani, and Masao Ikeda* 339

A Case of Coronary Sclerosis in Small Arteries Associated with Diffuse Myocardial Fibrosis. *Ryozo Okada, Kenichi Harumi, Masuyo Nomura, and Satoru Murao* 348

Number 4, October

Editorial: Present Status of Cardiology in Japan. *Hideo Ueda* 357

Balneotherapy for Hypertension with Special Reference to the Factor Analysis of the Effects of Spa Treatment on Hypertensive Patients. *Yoshio Oshima, Kosei Takahashi, Tsutomu Kashiwagi, Iwao Yokoyama, Toshiro Sato, Momosuke Hara, Ieo Akaoka, Ichiro Nishizawa, Tadashi Amamiya, and Masamori Maeda* . . 361

Open Heart Surgery under Hypothermia. *Itsuro Fukukei, Yōtarō Iyomasa, Shigeo Katō, Kinsaku Sakakibara, Hiroshi Satake, Toshio Abe, Richū Horigome, Ryūhei Tonomura, Tamotsu Nishizaki, Ariyoshi Sawa, Hiromichi Tsuchioka, and Takeshi Shimizu* 375

The Study on Plethysmocardiography—A Preliminary Report. *Hiroto Mashiba* 392

Electrocardiographic Changes in Open Heart Surgery under Hypothermia *Hiroshi Satake, Hiromichi Tsuchioka, Osamu Minamikawa, Toshihito Maehara, and Takeshi Shimizu* 397

Experimental Studies on Medionecrosis of the Aorta—Discussion on the Underlying Factors of Lathyrism, Ehlers-Danlos and Marfan's Syndromes. *Kunio Yamakawa, Kazuo Kitamura, Hiroshi Ohta, and Yoshiaki Noda* 408

Study on the Ventricular Activation of the Heart of Cattle and Goat. *Hiroshi Sugeno, Satoru Murao, and Hideo Ueda* 418

Algebraic Reflections on the Vector Concept in Electrocardiography. Part II. Structure of the Electric Field. *Mitsumasa Sato* 432

Special Article: Lung Blood Volume in Acquired Valvular Diseases. *Kiyoshi Fujimoto, Ryo Kunieda, and Takuya Shiba* 442

Case Reports: Hemoglobin M Disease—A Case Report. *Noboru Kimura, Shozi Nishimoto, Yoshio Nawata, Fuminobu Mori, Shunichi Kodama, and Shigeo Nakakura* 456

Annular Constrictive Pericarditis—A Case with Functional Pulmonary and Mitral Stenosis. *Tsuguya Sakamoto, Nobuyoshi Kawai, Jugoro Takeuchi, and Hideo Ueda* 466

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Editorial

Preface to the Publication of Japanese Heart Journal

In recent years, the number of basic and clinical studies in the field of cardiology has been accelerating at a rapid rate in Japan. These studies have been most beneficial not only from the standpoint of scientific development but also because they have resulted in the publication of articles which act as a stimulus to our fellow colleagues. However, since the majority of these articles have been written in Japanese, their contents have been confined to our shores and not exposed to the outside world; and, it seems that cardiological development in Japan has been left in the shadows—solely because of this language difficulty.

Having for some time recognized that the prime solution to this problem would be the Japanese publication of an English-written journal, I set about the task of soliciting the support of the most eminent cardiologists here in Japan. This, the first English publication of the Japanese Heart Journal, is evidence of the overwhelming and extremely gratifying response received.

For the present, the journal will be published quarterly and include the following:

a. Editorial

b. Original articles: Results of original study. Articles which appeared in Japanese medical journals but were not published in foreign language will also be included in this category.

c. Special articles: A series of outstanding investigations.

d. Case reports

It is my sincere hope that this publication will, to the rest of the world, serve as the "beacon light" of Japanese research and thereby extend our contribution to international advancements in the field of cardiology.

January, 1960

Hideo Ueda

Hideo UEDA, M.D.
Editor-in-Chief

Circulatory and Respiratory Changes Induced by Stimulation of the Thalamic Nuclei

Hideo UEDA, M.D.,* Soichi KATAYAMA, M.D.,
Hitoshi GOTO, M.D., *and* Kiyoshi ITO, M.D.

The purpose of this paper is to elucidate and to discuss the central regulation of circulatory and respiratory functions in the thalamus by electrical stimulation. The stimulation of the medial part of the thalamus—the midline, medial and anterior nuclei group—resulted in marked changes in blood pressure, cardiac beat, breathing and other visceral functions. But on stimulation of the ventral and lateral nuclei group, there occurred little or no change in the vegetative activities. These findings are well correlated with the information about the anatomical connections of thalamic nuclei. Therefore, this medial portion seems to represent the autonomic area in the thalamus.

THE thalamus is a relay station of the sensory system in the forebrain and is also responsible for the mechanisms of movement, emotion and consciousness. From the anatomical point of view, the thalamus was proved to have fiber connections with cortical and subcortical areas and the emphasis should be given to its connection with the hypothalamus, frontal cortex and limbic structures. Therefore, one might easily assume the participation of the thalamic nuclei in the vegetative functions.

Since the works of Karplus and Kreidl (1909–1927), most of the previous studies on the autonomic function of diencephalon focussed their interests mainly on the hypothalamus except the classic study of Sachs[1] (1911) on the thalamus.

However, first performance of thalamotomy by Spiegel in 1947 stimulated further experiments on the autonomic functions of the thalamus. Among them, Akert *et al.*[2] (1951), Baird *et al.*[3] (1952), Dell *et al.*[4] (1952), Misao *et al.*[5] (1954), Masaki[6] (1955), and Monnier[7] (1955) have been known. In these works there have been some confusions in the classification or nomenclature of the thalamic nuclei and some authors even did not clearly describe the sites stimulated. Therefore, the autonomic function of each thalamic nucleus remains to be thoroughly examined. For this reason, the authors made the following experiments.

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Materials and Methods

Twenty-five dogs were used in present experiments. Morphine chloride (6 mg./Kg.), or the combination of morphine chloride (3 mg./Kg.) with chloralose (50–70 mg./Kg.) were used for the anesthesia. By using the stereotaxic instrument, devised by the Institute of Brain Research, Faculty of Medicine, University of Tokyo, the stimulation electrode was placed. The location of the tip of this electrode was determined by histological control following each experiment. For precise localization of the stimulus, a bipolar concentric electrode was used and this electrode was completely insulated except for the tip.

The electrical stimuli were rectangular voltage pulses; their duration was 1 msec.; their voltage 1 to 6 volts (4 to 30 volts in crest value); and their frequency 100 cycles per second. Each stimulus was applied for approximately 30 seconds.

The blood pressure was recorded on a kymograph by means of a mercury manometer connected to the femoral artery. Electrocardiogram was taken on the standard leads I and III and the intraatrial lead. The effect of the myogram induced by convulsion was sometimes seen on thalamic stimulation which could interfere the EKG tracing. For this reason, an electrode was inserted into right atrial cavity in order to eliminate the myogram and to obtain a tall and clear cut picture of P-wave.

The respiratory movement of the thorax was registered on a kymograph by means of a tambour connected to the cuff wrapping around the thorax, and simultaneous recording was made with an ink-writing oscillograph using a transducer of rubber tube filled with zinc sulfate solution.

In this paper the nuclei of the thalamus are classified into five groups, namely the anterior nuclei, the nuclei of the midline, the medial nuclei, the ventral nuclei and the lateral nuclei group, according to the morphological studies on the diencephalon of carnivora by Rioch[8] (1936).

The intralaminar nuclei group is included in the medial nuclei group, and the following structures adjacent to the thalamus are excluded; the epithalamus, the subthalamus, the medial geniculate body and the lateral geniculate body.

Results

Sixty one different points in five nuclei groups of the thalamus were stimulated.

Circulatory and respiratory responses as well as other visceral and somatic changes obtained by this stimulation are shown in Table I to Table V. The results can best be stated by taking up each nucleus separately. Fig. 1 and 2 show degrees or types of responses and the stimulated sites in 7 diagrams of the frontal section of the thalamus.

Circulatory Responses—

Changes in blood pressure: In most experiments, changes elicited were pressor effects. Depressor effects were seen in a few points of the medial, ventral and lateral nuclei group. In Fig. 4 blood pressure changes are expressed as a ratio to the control level, and their degrees are divided into 4 stages. In-

Table I. Responses to Stimulation of the Anterior Nuclei Group

Stimulated site	No. of exp.	Blood pressure	Heart beat	Respiration	Other visceral & somatic changes
N. anterodorsalis	5	++	$S-T_1$, T_2 V.Es-B, Bl	–	None
N. anteroventralis	5	++~+++	A.Es	–	Mydriasis(1), Convulsion(1), Incontinence(1)
N. anteromedialis	2	0	0	–	None

Note:

1) Blood pressure responses are expressed as follows:
   - – Fall
   - 0 Little or no elevation (0~20% increase to control level)
   - + Slight elevation (21~40%)
   - ++ Moderate elevation (41~80%)
   - +++ Marked elevation (over 81%)

2) Changes in cardiac rhythm are shown in abbreviation as follows:
   - $S-T_1$ Marked sinus tachycardia (over 100% increase to basal rate)
   - $S-T_2$ Moderate sinus tachycardia
   - S–B Sinus bradycardia
   - V.Es–A Ventricular extrasystole with shorter coupling period
   - V.Es–B Ventricular extrasystole with longer coupling period
   - V–T Ventricular tachycardia
   - N Nodal ectopic beat
   - A.Es Auricular extrasystole
   - Bl Atrio-ventricular block

3) Patterns of respiratory change are divided according to the change of its frequency and amplitude.

Amp. \ Freq.	↑	0	↓
↑	+	+	+
0	+	0	–
↓	+	–	–

+: Acceleration
0: No change
–: Inhibition

4) The number in ( ) indicates the incidence of each sign.

crease of less than 20% is often followed by a gasping respiration and it is considered to have little significance. Increase of 21 to 40% indicates slight elevation, 41 to 80% moderate and over 81% marked.

As seen in Fig. 4, the midline and medial nuclei group stimulation yields the most prominent increase in blood pressure. Both groups show moderate to marked elevation in about two-thirds of the experiments and their threshold for the stimuli is low and even 1 to 2 volts elicited marked elevation of blood pressure. On midline nuclei stimulation, all experiments but one, showed blood pressure elevation with relatively strong stimuli (4 to 6 volts), but on the medial nuclei stimulation of same intensity caused little or no changes in 10 cases. The ventral and lateral nuclei were not clearly

Table II. Responses to Stimulation of the Midline Nuclei Group

Stimulated site	No. of exp.	Blood pressure	Heart beat	Respiration	Other visceral & somatic changes
N. commissuralis interparataenialis	1	biphasic	S-T_2	0	None
N. rhomboidalis	7	±~±±	S-T_2 V.Es-A, N	+~− Apneusis	Mydriasis (3), Urinary incontinence (1)
N. centralis medialis (N. reuniens)	8	+~±±	S-T_1, A.Es	+ Apneusis	Mydr. (5), Piloerection (3), Incontinence (3), Convulsion (8)
N. commissuralis interventralis	6	±~±±	S-T_2, A.Es Bl, V.Es-A	+	Convulsion (1)
N. paraventricularis anterior	7	±~±±	S-T_1, T_2 V.Es-A,B	0~+	Mydriasis (5) Convulsion (3)
N. paraventricularis posterior	2	±±	S-T_2, V-T V.Es-B	+ Apneusis	Mydriasis (2)
Periventricular system	8	±±	S-T_1, T_2 A.Es, Bl	+~−	Mydriasis (7) Convulsion (7) Piloerection (1)

Table III. Responses to Stimulation of the Medial and Intralaminar Nuclei Group

Stimulated site	No. of exp.	Blood pressure	Heart beat	Respiration	Other visceral & somatic changes
N. parataenialis	5	±	S-T_1, T_2 V.Es-A, A.Es	−~+	Mydriasis (3) Convulsion (1)
N. medialis dorsalis	14	0~±±	0~S-T_1, T_2 N V.Es-A,B, Bl	0~+ Apneusis	Mydriasis (3) Convulsion (3)
N. submedius	4	+~±	S-T_2 A.Es	+	Urinary incontinence (1)
N. tractus habenulo-peduncularis	3	±~±±	S-T_2 V.Es-A	+	None
N. parafascicularis	4	±~±±	S-T_1 V.Es-B, Bl	Apneusis +	Mydr. (4), Convul. (3) Urin. incont. (2)
N. paracentralis	14	+~±±	0~S-T_1 V.Es-B	−~+	Convulsion (2) Urin. incont. (1)
Centre médian	6	±±	S-T_1, T_2 V.Es-B	+ Apneusis	Convulsion (6) Piloerection (3) Mydriasis (5)
N. centralis lateralis	4	−~0	0~S-T_1	0~−	None

responsive. Patterns of blood pressure elevation were variable, but most of them showed abrupt increase to the near maximal level instantaneously with stimulation, and continued to rise slowly during stimulation, and at the end of the stimulation they greatly decreased in their magnitude and then gradually

Table IV. Responses to Stimulation of the Ventral Nuclei Group

Stimulated site	No. of exp.	Blood pressure	Heart beat	Respiration	Other visceral & somatic changes
N. ventralis, pars anterior	6	0∼− ∼+	0∼S-T_2	0∼+	Mydriasis (2) Convulsion (2)
N. ventralis, pars medialis	3	+	S-T_2	−∼+	None
N. ventralis, pars externa	5	0∼++	S-T_1, T_2	−∼+	Mydriasis (4) Convulsion (4)
N. ventralis, pars arcuata	4	+	S-T_1	+	Mydriasis (3) Convulsion (3)

Table V. Responses to Stimulation of the Lateral Nuclei Group

Stimulated site	No. of exp.	Blood pressure	Heart beat	Respiration	Other visceral & somatic changes
N. lateralis, pars anterior	2	0	0	0∼−	None
N. lateralis, pars intermedia	2	0	0	0∼−	None
N. lateralis, pars posterior	6	−∼+	A.Es	−∼+	Convulsion (1) Mydriasis (3)
N. reticularis	2	+∼++	S-T_2 N	−	Convulsion (2) Mydriasis (1)

returned to the basal level. In a few cases, however, after cessation of the stimulation the blood pressure decreased to the basal level but ascended again with clonic convulsion.

Changes in cardiac beat: Acceleration of cardiac rate was observed in most of the cases, and cardiac inhibition was rarely encountered on thalamic stimulation. Fig. 5 shows changes in heart rate yielded on each thalamic nucleus stimulation. It is expressed as a ratio (%) of the heart rates for each 10 seconds before and during stimulation. In 18 out of 39 cases of midline nuclei stimulation and in 8 out of 31 cases of medial nuclei stimulation, there appeared marked tachycardia indicating over 100% increase of the basal rate. On the stimulation of other nuclei groups, cardiac acceleration was in a lesser degree. In 6% of all experiments performed upon some regions of the anterior, medial and lateral nuclei, mild cardio-inhibitory responses were obtained.

Various arrhythmias such as supraventricular and ventricular extrasystole or escape and atrio-ventricular block etc. were also observed. Ueda *et al.*[9] (1959) reported that ventricular arrhythmias induced on electrical stimulation of the brain stem might be divided into two types ("A" and "B") according to their EKG features and modes of appearance. On thalamic

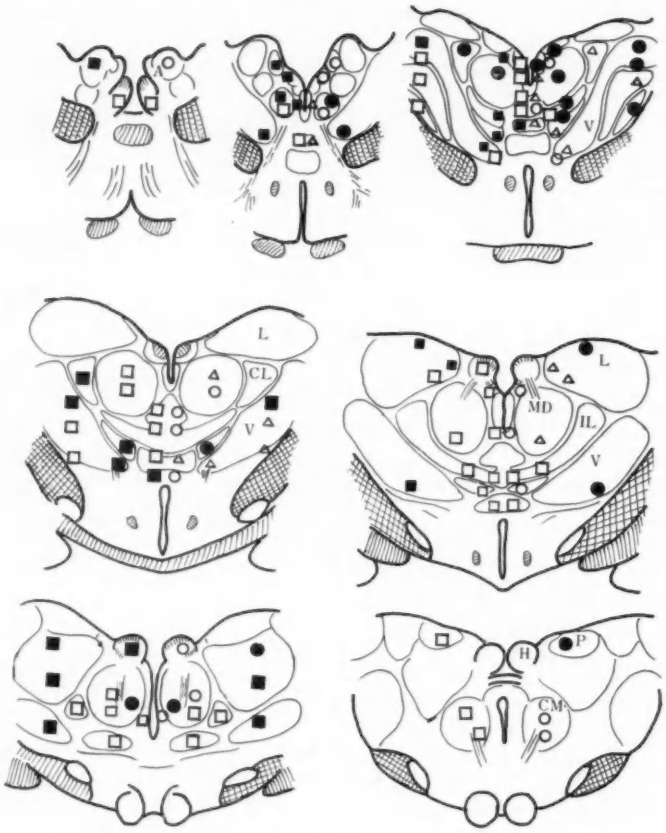

Fig. 1. Mappings of the stimulated sites at which vasomotor and respiratory effects were obtained. Vasomotor effects on the right side of each diagram, respiratory effects on the left side. Symbols are as follows.

Respiratory effects	Blood pressure responses
Acceleration	□ Marked elevation
	○ Moderate elevation
	△ Slight elevation
No change	● Little or no change
Inhibition	■ Fall

A: N. anterior
CL: N. centralis lateralis
CM: Centre médian
H: Habenula
IL: Intralaminar nuclei
L: N. lateralis
MD: N. medialis dorsalis
P: Pulvinar
V: N. ventralis

stimulation both type A and B were found. Type A, with shorter coupling period (usually 0.20–0.30 sec.), frequently appears in the early period of stimulation and tends to appear in the inspiratory phase independently of blood pressure elevation. This type of extrasystole was elicited on stimulation

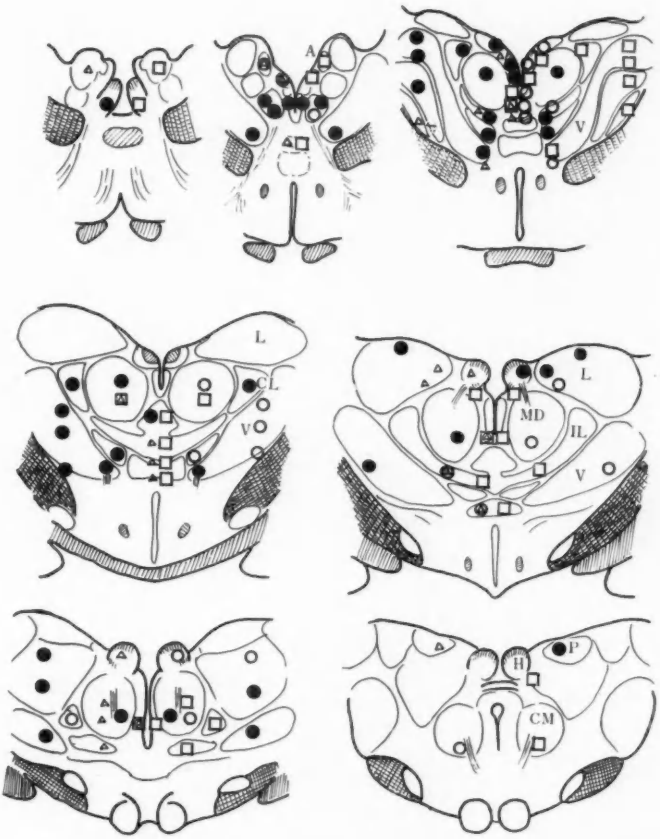

Fig. 2. Mappings of the stimulated sites at which changes in heart beats were obtained. Changes in heart rate on the right side of each diagram, types of arrhythmia on the left side. Symbols are as follows.

Types of arrhythmia	Changes in heart rate
V.Es-A	□ S-T_1
V.Es-B	○ S-T_2
Others	△
Not elicited	● No change
	■ S-B

A: N. anterior
CL: N. centralis lateralis
CM: Centre médian
H: Habenula
IL: Intralaminar nuclei
L: N. lateralis
MD: N. medialis dorsalis
P: Pulvinar
V: N. ventralis

of the medial portion in the brain stem in general, and in the thalamus it occurred only on stimulation of the nuclei of midline and medial nuclei group. Type " B " extrasystole with longer coupling period (usually more than 0.30 sec.), simulating escaped beat because of its occurrence with prolongation of

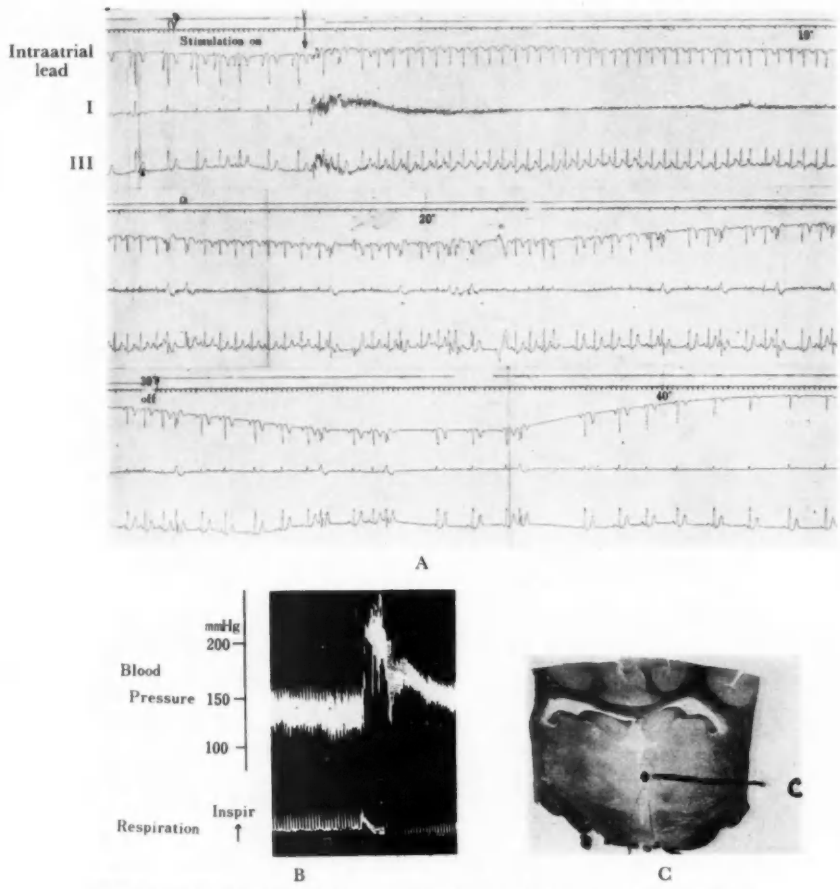

Fig. 3. Records of stimulation on midline nuclei (Dog No. 19, Exp. 20).
A: Electrocardiographic tracings taken on intraatrial lead and standard lead I and III.
B: Kymographic records of blood pressure and respiratory responses.
C: Frontal section of thalamus indicating the site of stimulation (C: Nucl. paraventricularis anterior).

P-P and/or P-R interval, occurred when a relatively widespread region of the brain stem was stimulated. In the thalamus, it also was observed on stimulation of the anterior nuclei besides the above mentioned two nuclei groups. On stimulation of the ventral and lateral nuclei groups, few arrhythmias were yielded.

Respiratory Responses—

Changes in respiration are classified in the notes given under Table I. Besides them apneusis was also included. The results are shown in Table I

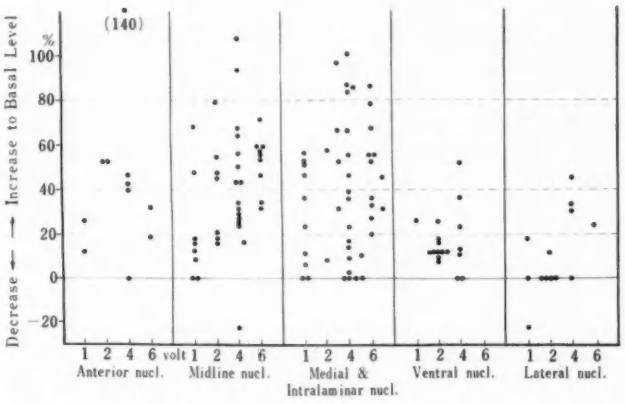

Fig. 4. Blood pressure responses after stimulation of different thalamic nuclei.

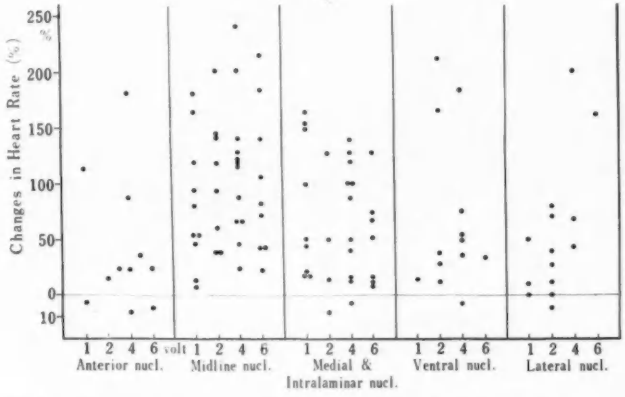

Fig. 5. Changes in heart rate after stimulation of different thalamic nuclei.

to V, and on the left side of each diagram in Fig. 1.

On stimulation, the midline and medial nuclei yielded mainly facilitatory responses but in a few cases respiratory inhibition was also found on stimulation of nuclei such as nucl. rhomboidalis, periventricular system, nucl. parataenialis and nucl. centralis lateralis. From the ventral nuclei there occurred both facilitatory and inhibitory responses, and from most of the lateral nuclei, inhibitory ones. In all cases of anterior nuclei stimulation, there appeared a marked inhibition of respiration.

Inspiratory apnea due to tonic convulsion was seen in some experiments, and the respiratory patterns in these cases are difficult to be decided whether facilitatory or inhibitory.

Other Visceral and Somatic Signs—

Besides circulatory and respiratory responses, visceral signs such as pupillary change, exophthalmos, incontinence of urine or feces and piloerection were observed. Pupillary change, in most cases mydriasis, and exophthalmos were yielded from any thalamic nuclei stimulation, but piloerection, though infrequent on thalamic stimulation, was localized only to midline and medial nuclei stimulation. From anterior nuclei other than these two, urination and defecation was yielded.

As to somatic signs, tonic convulsion occurred in some cases of midline, medial and anterior nuclei stimulation, but less in other nuclei groups. By stimulating nucl. ventralis pars arcuata, centre médian, nucl. medialis dorsalis, nucl. paracentralis and nucl. paraventricularis anterior, a clonic convulsion was observed following tonic convulsion before or after the end of stimulus.

Various Responses with the Change of Stimulation Parameter—

Intensity of stimulus: The threshold to stimuli was variable because of different excitability in each nucleus. Fig. 6 shows how blood pressure response varies when the intensities of stimulus are modified in two cases of different threshold. As to the change in heart rate, the same tendency was noted (Fig. 7). Generally speaking, in the midline and medial nuclei group the threshold was low (see Fig. 4 and 5).

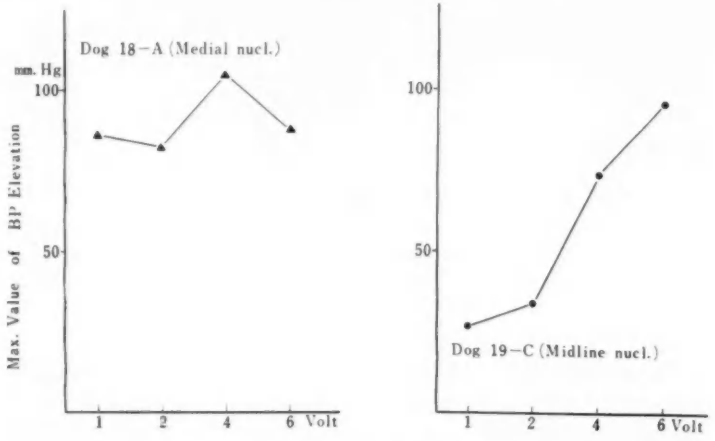

Fig. 6. Blood pressure responses to electrical stimulation of various intensities.

Frequency of stimulus: The kymographic records seen in Fig. 8 show remarkable changes in blood pressure and respiratory response to various frequencies of stimulus (other parameters remained constant). In this case, the adequate frequency lies between 60 to 100 cycles per second. In our experiment, relatively high frequency, chiefly 100 c/s, was used throughout

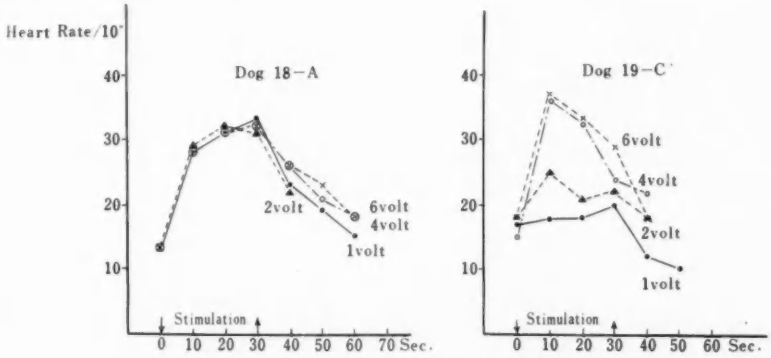

Fig. 7. Changes in heart rate on various intensity stimulation.

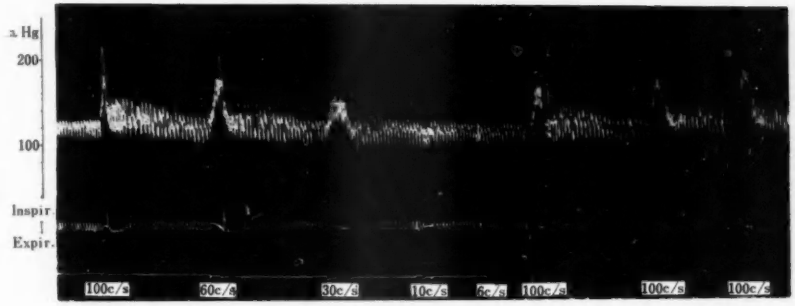

Fig. 8. Blood pressure and respiratory responses to various frequency stimulation of thalamic nuclei (midline nucl.).

the study, and this might be a cause of rare incidence of depressor effect.

Discussion

The participation of the thalamus in the autonomic functions is inferred on the following grounds.

a) Clinical; " thalamic syndrome " involves the various autonomic signs and symptoms as reported by Vincent (1908), Bechterew, Schüster[10] (1936), van Bogaert[11] (1949) and Okinaka *et al.*[12] (1953) etc.

b) Neuroanatomical; the thalamus has fiber connections with the " visceral brain " as demonstrated by the retrograde degeneration method and physiological neuronography. The details will be referred to, in the following pages.

c) Physiological; the stimulation or destruction of the thalamic nuclei in animals may cause changes in autonomic functions. This is the very problem with which the authors dealt in this paper.

Since Danilewsky (1875) claimed that certain regions of the thalamus

were concerned with changes in blood pressure and pulse rate, a number of other observers have directed their investigations towards this subject. Sachs[1] (1911) was the first one who attempted to clarify their localizations. He noticed the elevation of blood pressure and changes in respiration by stimulating the various portions of the thalamus, but he ascribed these phenomena to the excitation of afferent nerve fibers of thalamic nuclei and said "there is no necessity for invoking the existence of special centers." In his paper the portions inert to stimulation were the median nuclei and the upper anterior end of the lateral thalamus. Since this work, almost no investigation of the thalamic autonomic functions was carried out.

However in recent years, Akert *et al.*[2] (1951) observed forced respiration by electrical stimulation of the anterior portion of the thalamus in unanesthetized cats. Baird *et al.*[3] (1952) reported that electrical stimulation of the anterior nuclei of the anesthetized cats and human revealed respiratory inhibition and mostly depressor effects on blood pressure. As for the changes in breathing, Dell *et al.*[4] (1954) showed that stimulation of nucl. ventralis anterior yielded a slowing down of respiration rate, and occasional apnea in some cases. In Japan, Misao & others[5] (1954) investigated the effects on peripheral blood picture, electrocardiogram and electrocorticogram by electrolytical destruction of the subcortical area, but failed to elicit electrocardiographic changes from the posterior nuclei. Masaki[6] (1955) stimulated the anterior nuclei and the medial region of the posterior thalamus chemically and observed blood pressure elevation, respiratory inhibition and other vegetative signs such as mydriasis, salivation and piloerection. Monnier[7] (1955) reported a case of electrical stimulation of the human thalamus and observed hyperpnea, tachycardia and thirst from the "région médiane" which consisted chiefly of intralaminar structure and was surrounded by "n. ventro-postéro-médiane," "n. dorso-médiane" and "centre médian." He correlated this phenomena with hypothalamo-thalamic connection. Korteweg[13] (1957) described the electrocardiographic changes on subcortical stimulation. In his study, an electrical stimulation of the thalamus, though its localization was undetermined, caused no disturbances in cardiac rhythm but showed blood pressure response at a minimum level and a slight change in the T-wave. The respiratory acceleration was also noted. From the review of previous literatures, apparently no extensive and systematic investigations of thalamic autonomic functions have been carried out. In this regard, the present study was done and an attempt was made to discuss the results with special reference to anatomical connections between thalamic nuclei and the "visceral brain."

Anterior Nuclei Group—(Table I, Fig. 1 and 2)

This nuclei group consists of anterodorsal, anteroventral and anteromedial elements. Pressor effect of this nuclei was reported in the papers of Sachs and Masaki respectively, but Baird declared that depressor effect was the rule. Our opinion is in accordance with that of the former. We found the respiratory responses were inhibitory in nature as in all previous studies.

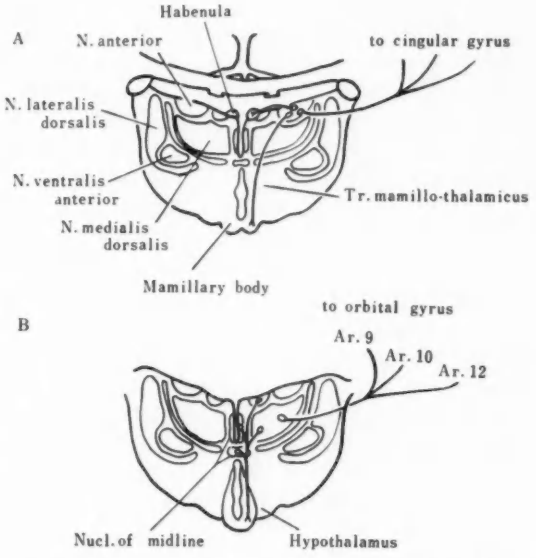

Fig. 9. Hypothalamo-thalamo-frontal connections (Modification of the figure of Hoff & Osler[14]).

In our experiment, acceleration in cardiac rate, arrhythmia of various types, mydriasis, urinary incontinence and convulsion were observed.

As seen in Fig. 9–A, the afferent impulses arising mainly from the homolateral mamillary body reaches the anterior thalamic nuclei via the mamillothalamic tract of Vicq D'Azyr. Changing the neuron at that site, the fibers project into specific cortical areas. The anteromedial element projects to the anterior part of the cingulate gyrus (Area 24) and perhaps to Area 32; the anteroventral element sends its fibers mainly to the posterior part of the cingulate gyrus (Area 23) and partly to Area 24; and the small anterodorsal element projects to the retrosplenial region (Area 29) of the cortex (Mitchell[15]). Area 24 is known to be a suppressor in nature and stimulation of this area produced alterations in the heart rate, blood pressure and respiration (Mitchell[15]). Since both mamillary body and cingulate gyrus have a connection with the other limbic system, Papez (cit. from Le Gros Clark[16]) suggested the following anatomical circuit which may maintain a continuous cycle of functional relationship between the hypothalamus and neopallial cortex, that is;

hippocampus→fornix→mamillary body→anterior thalamic nucleus→ cingulate gyrus (limbic cortex)→cingulum→hippocampus

Thus the anterior thalamic nucleus, member of this circuit, may be concerned with complicated integration of both autonomic and somatic systems in cortical and subcortical levels.

Midline Nuclei Group—(Table II, Fig. 1 and 2)

This group consists of a number of nuclei occupying massa intermedia and periventricular grey matter, and is in contact with the hypothalamus particularly tuber cinereum through the periventricular fiber system (Gurdjian) which is mainly unmyelinated and lying close to the ependyma of the third ventricle (Niimi[17]).

Therefore this nuclei group must have some functional relation with the hypothalamus. We noticed the most striking responses on the stimulation of this group. In approximately 50% of the cases, moderate to marked rise of blood pressure, and marked acceleration of cardiac rate were seen. Various types of arrhythmia, including ventricular extrasystole of type A, and respiratory facilitation or apneusis were observed. Besides circulatory and respiratory changes, other visceral and somatic signs appeared. Fig. 3 shows the results of stimulation of the midline nuclei. The electrical stimulus of 100 c/s, 1 msec. in duration and 6 volts caused blood pressure elevation of 86 mm. Hg. This caused also rapid respiration, and disturbances in cardiac rhythm such as sinus tachycardia, supraventricular and ventricular extrasystoles with a short run or trigeminy. The nuclei of this group are small and poorly defined so that their responsiveness remains to be unnoticed by most of the investigators except Sachs who observed moderate to marked rise of blood pressure and inspiratory inhibition associated with forced inspiration, though the pulse rate did not change on the stimulation of nucl. reuniens. But he did not make any remarks about its significance.

Medial Nuclei Group and Intralaminar Nuclei Group—(Table III, Fig. 1 and 2)

In this experiment, these areas next to the midline nuclei group revealed marked visceral responses on stimulation. However, Sachs observed neither respiratory nor circulatory changes on the stimulation of nucl. medius. Accoring to Misao, there appeared no electrocardiographic change on medial nuclei stimulation. Only Monnier suggested the hypothalamo-thalamic correlations on the ground that stimulation of " région médiane " called forth respiratory and cardiac acceleration.

In these papers, the nomenclature of the nuclei is not always definite and it is difficult to compare them with our results.

The anatomical relations of the medial nuclei group to the hypothalamus or frontal cortex were clarified by the human or animal leucotomy and electrophysiological studies. The principal part of the medial (dorso-medial) nucleus, the pars parvicellularis, has widespread connections with the frontal cortex such as the orbital region (Area 11 and 47), inferior and middle frontal gyri (Area 45, 46 and probably 6) and superior frontal gyrus (Area 8); and the pars magnocellularis of the medial nucleus sends fibers to Area 11 and 12 in the orbital region. The hypothalamus is linked with medial thalamic nuclei, particularly with its pars magnocellularis, through the periventricular system of fibers of the third ventricle, and the medial nuclei are essentially relay station for the onward transmission to the frontal cortex of

impulses originating in the hypothalamus (Mitchell[15]). Recently, Droogleever Fortuyn and others[18] (1959) found a strong fiber connection from the rhinencephalic structures at the base of the telencephalon towards the parataenial and dorsomedial nucleus of the medial nuclei group.

It is therefore justifiable to assume that in regard to these hypothalamo-thalamo-cortical connections the medial nuclei are concerned with autonomic functions besides mental and emotional activities. This hypothesis is proved to be true in this experiment.

Ventral Nuclei Group—(Table IV, Fig. 1 and 2)

This group is relay nuclei of the sensory system to cortex. In this nuclei group we found slight changes in circulatory functions following stimulation, and respiratory responses were variable though their degree was minimum. Sachs stated, however, that the stimulation of nucl. lateralis ventralis yielded a moderate to marked pressor effect in two-thirds of all experiments. Respiratory inhibition was the rule. He mentioned these results were similar in every respect to those observed when an afferent nerve is stimulated, therefore he ascribed them to reflex effects. Dell observed inhibition of breathing, and Misao could not elicit any change in the cardiac beat on this nuclei stimulation.

Lateral Nuclei Group—(Table V, Fig. 1 and 2)

The function of this nuclei group is not clearly known, but is assumed to be association nuclei in thalamus. In the present experiment, circulatory changes were scarcely obtained and respiration was slightly suppressed. Our results, on the whole, agreed with that of Sachs.

The latter two nuclei groups were more inert to stimuli as regards the visceral functions than other nuclei groups. Apparently it is due to the fact that they have no anatomical connections with the "visceral brain."

From the results shown above, the autonomic respresentation in the thalamus was demonstrated in the medial portion of the thalamus—the midline, medial and anterior nuclei group.

In the authors' opinion, these findings are well correlated with the information about the anatomical connections.

Summary

Circulatory and respiratory function of the thalamus was studied in 25 dogs and the following results were obtained.

(1) Marked elevation of arterial blood pressure was observed by the stimulation of the midline nuclei group and medial nuclei group. Stimulating the anterior nuclei group, slight vasopressor responses were found. But the stimulation of the ventral and lateral nuclei group caused little change in blood pressure.

(2) The standard and intraatrial lead of electrocardiogram showed marked acceleration of cardiac rate and various arrhythmias such as nodal extrasystole or escape and ventricular extrasystole etc. by the stimulation of

the midline and medial nuclei group and some portions of the anterior nuclei group. These ventricular extrasystoles were divided into 2 groups according to their characteristics in EKG and the regions causing each of them were also discussed. The stimulation of the ventral and lateral nuclei group scarcely resulted in any disturbances of the cardiac rhythm.

(3) Acceleration of breathing was shown on the stimulation of the midline, medial and ventral nuclei group. All cases of the anterior nuclei stimulation elicited marked inhibition of respiration.

(4) Other visceral and somatic changes such as pupillodilatation, erection of hair, urinary or fecal incontinence and convulsion were observed upon the stimulation of various regions in the thalamus, but they occurred most prominently on the midline and medial nuclei stimulation.

From the data above-mentioned, it can be concluded that the stimulation of the medial part of the thalamus—midline and medial nuclei group—results in marked changes in circulation, respiration and other autonomic functions. Furthermore, considering the anatomical relationship between the thalamic nuclei and the higher autonomic centers, it seems that the autonomic representation in the thalmus locates in this portion.

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The Study on Hepatic Blood Flow Determination by Au^{198} Colloid Using Deviced Recording Method

Part I. New Apparatus for the Determination of Circulation
Part II. Determination of Hepatic Blood Flow

Masahiro IIO, M.D., Haruo KAMEDA, M.D.,
and Hideo UEDA, M.D.*

Hemodynamic studies using radioactive isotope have become popular in recent years, however, besides many technical difficulties and hazards the accuracy of determination is doubtful. In view of these, the authors deviced a simple recording apparatus which is able to measure the radioactivity simultaneously and accurately at different portions. With this method control cases and various diseases were examined to determine their hepatic blood flow, and determinations were also made after administration of many drugs or blood transfusion. It was proved that this method was very accurate and useful for the clinical purpose.

Part I. New Apparatus for the Determination of Circulation

AT the present time, many methods have been used for the study of hemodynamics. However, most of these methods were not practical for the clinical use, and there is sometimes danger to the patient during their use. Recent improvement of radioisotope (R. I.) technique has been applied in many fields of medical research, including hemodynamic studies, without great risk to the patients. If the activity of R.I. can be accurately determined by the external counting method, it seems that this method could minimize the burden of the patient and it appears also possible to repeat the determination at adequate intervals when necessary. However, the difficulty is that the commonly used external counting method is not quite suitable for the simultaneous determination of R.I. at two or more different portions of the body. It is also desirable to record some electrical phenomena such as pressure, respiratory curves and electrocardiogram simultaneously if it is possible. MacIntyre and his associates[20] applied a rate counting computor for the determination of cardiac output. This method was an advanced one, however this was expensive and inadequate for the purpose of multi-recording. In view of these, we deviced a new multi-channel recording system which is simpler and gives a better accuracy than previously used recording systems, mainly rate-meter.[3)-6)] The authors' new multi-channel-recorder is shown as a schematic drawing in Fig. 1.

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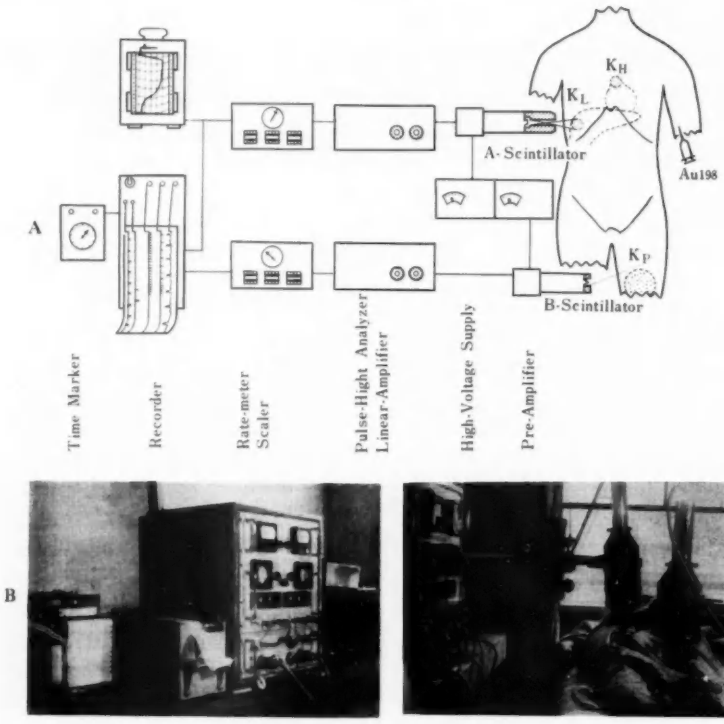

Fig. 1. A (upper): Schema of the experimental apparatus.
B (below): Photograph of the apparatus.

Each scintillation detector consists of a $1\frac{1}{2}$ inch (diameter) $\times 1$ inch (depth) talliated sodium iodide crystal (Harshaw Chemical Co.) coupled to a photomultiplier tube (RCA 6199). The crystal detector was collimated with a lead cylinder. The detector is set up in such a way that each of the two heads can be easily moved manually over any portion of the patient.

The pulse-height-analyzer is used in each circuit in order to remove radioactivity such as scattering γ-rays from neighbouring organs and background. This would also make it possible for us to utilize two different isotopes simultaneously or successively on the same subject.

The impulses from the pulse-height-analyzer go through a scaler* (Riken KC-I), and after the collection of a predetermined number of counts (10, 100 or 1000. Usually 100 counts are used), galvanometer-type pen-recorder makes a mark on the recording paper, which has a constant speed of 1, 3 or 6 cm./sec. or 1, 3 or 6 mm./sec.

The advantages of this recording method are as follows.

* Through the Physical and Chemical Institute of Japan.

(1) An interval of each mark on the paper represents the time of the collection of a predetermined number of counts. This differs from the rate-meter method used in previous studies in which there is some influence on the true reading by the previous counting rate. Thus the figure of activity against the time could be shown on the semi-logarithmic paper by successively converting interval of the marks into a counting rate (c.p.m.). In this procedure, smoothing the graph can be obtained by taking an average of intervals of three or more markings.

(2) The record of the activity in a case of longer duration is also accurately obtainable by multiplying the minute volume of markings by one hundred. This method also offers the quick and accurate determination of any changes in activity during the course of static phenomenon.

(3) Since the multi-channel recorder is used in our experiment, it is possible to record electrocardiogram, phonocardiogram, respiratory rate and pressure simultaneously with the changes in the activities at different portions of the body. This is of particular value in the study of the heart, permitting a more precise analysis of hemodynamics.

(4) Paper speed could be changed within the range from 1 mm. to 6 cm. per second according to the degree of the counting rate, or to the speed of the hemodynamic changes. This is especially convenient in the cases, where several runs of examination are required, such as in cardiac output examination etc.

The conventional counting rate-meter (time constant 1 second or 40 second, counting range $0–10^3$, $0–10^4$, $0–10^5$ c.p.m.) was also used for the purpose of monitoring, but the record of this was not applied in the calculation. Time marker (1, 15 or 30 seconds) is set up, allowing for automatic recording. Another circuit and adaptor for the Geiger-Müller (G.M.) counter is also built in this scaler, and this apparatus could be applied also for the study of hemodynamics using catheter-type micro G.M. tubes.

Part II. Determination of Hepatic Blood Flow

In 1952, Dobson and Jones[1] described a method of hepatic blood flow determination using P^{32} labelled colloidal chromic phosphate, and lately Vetter and co-workers (1954)[4] and Krook (1956)[3] simplified this method by using Au^{198} colloid, permitting external determination of the disappearance-rate-constant K. After these reports, many studies were carried out in Japan. The method of determining Au^{198} colloid disappearance-rate-constant from the periphery was usually used and it was believed to represent an accurate hepatic blood flow. However, in case of congestive heart failure and splenomegaly where abnormal diffusion and/or accumulation of Au^{198} colloid exist, the accuracy of this method is doubtful. Therefore, an attempt was made to compare the values of hepatic blood flow in above mentioned cases

obtained by the previously described method with those of our method.

Up to lately, hepatic blood flow determination by Au^{198} colloid was made mainly on cirrhosis and no previous investigations have been attempted on the various diseases other than cirrhosis. The authors studied many cases of various diseases, paying particular attention to cardiac failure and so on.

In addition, hepatic blood flow was determined not only in the fasting state but also in conditions where acute hemodynamic changes were induced experimentally. These studies were possible to be accomplished by our new recording method which could allow both good response and accurate counting rate continuously.

Materials and Methods

A total number of 152 cases admitted to the 2nd Department of Internal Medicine, Tokyo University Hospital during 1958–1959 are studied. This number of cases consists of 29 controls and remaining 123 with various diseases. These 123 diseased individuals consist of 24 cases of liver cirrhosis, 9 of Banti's syndrome, 17 of congestive failure, 11 of various types of jaundice, 8 of gall bladder disease, 5 of hepatic carcinoma, 16 of nephritis, 5 of hypertension without cardiac failure, 3 of emphysema, 5 of thyroid disease, 9 of malignant tumor and 11 miscellaneous cases (Fig. 5).

The subjects including controls were examined in a fasting state in a supine position. Radioactive colloidal gold was administered rapidly by intravenous injection and continuous recording was made over a 40 minute period. The quantity of particulate material should not exceed 250 μg. according to Vetter.[4] In our determination, γ-rays of lower energy, including scattering γ-rays and background were eliminated by pulse-height analyzer. Three portions within the body were selected for the determination of radioactivity. As illustrated in Fig. 1, head A (collimated with a lead cylinder 3 cm. thick, 7.5 cm. in length and having an aperture 3 cm. in diameter) was placed against the skin of the chest wall over the cardiac base and/or over the distal part of the liver avoiding any interference from other major organs. From heart region, Au^{198} colloid disappearance-rate-constant (K_H) of the rapid circulating phase is ascertained, and from the liver region the accumulation rate constant (K_L) is calculated. Head B (uncollimated scintillation probe with 3 cm. of lead surrounding the head case to eliminate any scattering from the liver) was placed over the distal part of one thigh in proximation with the skin according to the method of Krook.[3] From this portion the disappearance rate constant of the periphery (K_P), including the slow circulating phase of the capillary are calculated. The simultaneous use of the combination of any two rate-constants were determined interchangeably in all cases (K_P-K_H, K_P-K_L, K_H-K_L). Fifty micro curies were used as a dose to obtain a satisfactory recording from any area of the body.

As the gradual changes in the activity were recorded continuously as the changes in the frequency of markings on the paper, the counting rate (c.p.m.) at any time could be expressed by summation of these markings during one minute interval multiplied by 100 (usually 100 counts were predetermined). Then this counting rate was plotted on a semi-logarithmic paper against the time. Analysis of the original

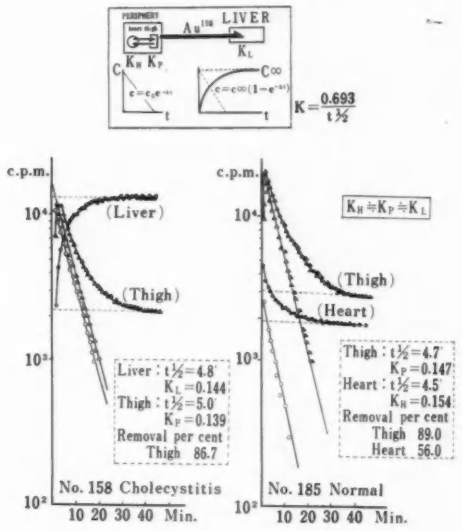

Fig. 2. Record of external counting of Au^{198} colloid on the liver, thigh, and heart. Calculations of K_L, K_P and K_H are illustrated.

curve to obtain the first exponential component was made graphically as in Fig. 2, according to the method of Dobson and Vetter.[1)4)] The slope of the curve C_0e^{-kt}, K_H or K_P, was calculated by the formula $K=0.693/t\frac{1}{2}$, where $t\frac{1}{2}$ was the half time of the decrease of the first exponential component derived from a simple subtraction of a slow component from the original curve at any time. The value of K_L is calculated by a subtraction of the original curve $C\infty\ (1-e^{-kt})$ from the activity level reached in infinite time $C\infty$, thus converting the integral curve into a rate curve of accumulation $C\infty e^{-kt}$ [1)8)]. The value of K_L could be calculated according to the same way as described above. The authors made this calculation based on the precise counting index, derived from the recording paper, so that the calculations could be more accurate and more points could be plotted on the graph in comparison to the previously described method by others.

In a few cases, blood samples were withdrawn simultaneously and this sample was counted in a well-type scintillation counter. In some cases immediate and succeeding determinations of hepatic blood flow were made, and in others it was made with one month interval by the external counting method in order to determine reproducibility.

Determination of the disappearance rate constant K was made on a total number of 180 times in 14 different group of patients.

In 40 of these cases, hepatic blood flow (ml./min.) was calculated multiplying K by total blood volume (T-1824 method).

An attempt was also made in 29 cases, in which the disappearance rate constant (K) was experimentally changed by applying various procedures, such as blood transfusion or drug administration, and the physiological significance of various factors in these procedures was studied.

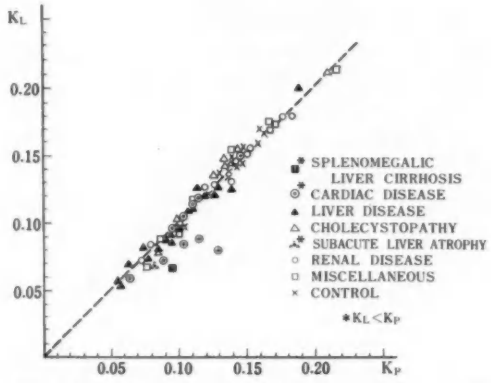

Fig. 3. Correlation between peripheral disappearance rate constant (K_P) and liver accumulation rate constant (K_L).

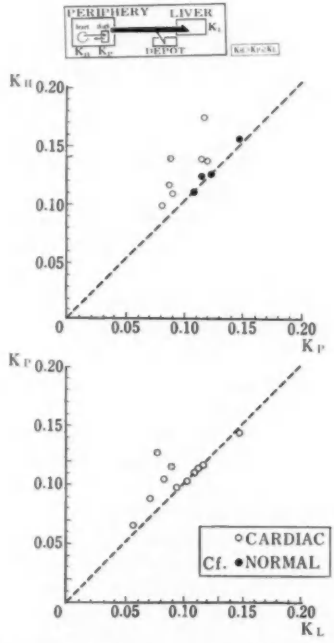

Fig. 4. Correlation between disappearance rate constant K_H and K_P (-upper), K_P and K_L (-below), in patients of cardiac disease.

Results

(1) The correlations between three disappearance rate constants (K_H, K_P and K_L)

Table I. Comparison of Disappearance Rate Constant by External Counting (K_H, K_P, K_L) with Constant by Simultaneous Venous Sampling (K_V)

No.	Disease	K_H	K_P	K_L	K_V
184	Nephritis	0.187	0.187		0.161
185	Normal	0.154	0.147		0.147
186	Combined valvular disease	0.138	0.089		0.114
188	Pericarditis	0.115	0.087		0.096
187	Cirrhosis		0.067	0.068	0.060

Note: Venous blood is counted by well-type scintillation counter.

Table II. Reproducibility of Disappearance Rate Constant (K)

A: Determination of one hour interval

No.	Disease	K_1	K_2	K_3
88	Reticulo-sarcoma	0.133	0.122	
89	Pseudo-myxoma	0.107	0.103	
91	Carcinomatous peritonitis	0.102	0.098	
110	Combined valvular disease	0.095	0.106	0.095
163	Nephritis	0.148	0.148	

B: Determination of one month interval

		K_I	K_{II}	K_{III}
87	Early cirrhosis	0.096	0.087	
92	Hemochromatosis	0.057	0.060	
125	Early cirrhosis	0.120	0.116	0.105
134	Mitral valvular disease	0.115	0.103	
150	Hypertension	0.123	0.126	
163	Nephritis	0.148	0.147	
100	Emphysema	0.093	0.072	
153	Early cirrhosis	0.123	0.104	

In cases without cardiac failure or splenomegaly, the interrelations of disappearance rate constant $K_H \fallingdotseq K_P \fallingdotseq K_L$ was found (Fig. 2, 3 and 4). However, in cases of cardiac failure relation of $K_H > K_P \geqq K_L$ was noted. Also in one case of liver cirrhosis with splenomegaly K_P was larger than K_L.

(2) Comparison of two different K obtained by external method and the venous sampling method

The disappearance rate constant from the peripheral vein (Kv) was determined in 5 cases along with the determination of K_H, K_P or K_L by external method. The value of Kv was smaller than K_H, K_P or K_L in 3

cases, however, the relation of $K_H > K_V > K_P$ was found in 2 cases of cardiac failure (Table I).

(3) Reproducibility of K

In 5 cases, successive K determinations were carried out. Table II (A) shows these findings, where $K_1 \fallingdotseq K_2 \fallingdotseq K_3$ and $\Sigma\ (K_1 - K_2)/5 = +0.0016$, K_1 is somewhat larger than K_2 but this still falls within the range of calculation error. In 8 cases, repeated runs of K determination were performed one month later. The results are also indicated in Table II (B). In 6 cases $K_I \fallingdotseq K_{II} \fallingdotseq K_{III}$ and $\Sigma\ (K_I - K_{II})/6 = +0.0033$ are observed. Here the value of K_I is also larger than K_{II}, but not significant in degree.

(4) K values of various diseases

The results are shown in Fig. 5. In the control group, the disappearance rate constant (K) ranged from 0.100 to 0.203 with a mean of 0.146±

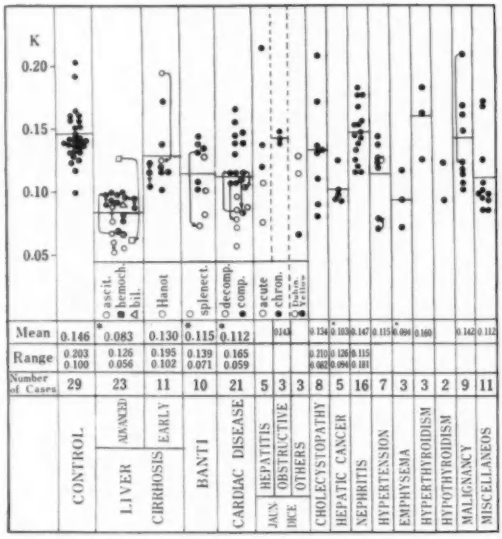

Fig. 5. Au^{198} colloid disappearance rate constant (K) in various diseases.

Note: * : Significant difference ($P<0.05$) compared with the mean value of the controls.

ascit. : Cirrhosis with ascites
hemoch. : Hemochromatosis
bil. : Biliary liver-cirrhosis
Hanot : Primary biliary cirrhosis of Hanot
splenect. : Splenectomized cases with Banti's syndrome
decomp. : Decompensated cardiac disease
comp. : Compensated cardiac disease
acute : Acute hepatitis
chron. : Chronic hepatitis
Dubin : Dubin-Johnson syndrome
yellow : Subacute yellow liver atrophy

0.008. In advanced group of cirrhosis, K varied from 0.056 to 0.126 with a mean of 0.083 ± 0.019, and in the Banti's group K ranged from 0.071 to 0.139, the mean being 0.115 ± 0.018. Statistically, these means showed a definitely decreased value as compared with the controls ($P<0.05$). The early stage of cirrhosis showed a value from 0.102 to 0.195 with a mean of 0.130 ± 0.019, and the difference from the control was not significant, but the difference between this early cirrhosis group and the advanced group was statistically significant ($P<0.05$). In cardiac group, the cases with failure showed a decreased value of K varying from 0.059 to 0.110 with an average of 0.086 ± 0.012, however the cases without failure had values between 0.107 and 0.165 with a mean of 0.121 ± 0.011. The K value of the decompensated group was significantly lower than the compensated group or the control ($P<0.05$). In nephritis group the value of K varied from 0.115 to 0.181 with a mean of 0.147 ± 0.012, the difference from the control being not significant ($P<0.05$).

Cases showing lower value than the normal limit were 96% of cases with advanced cirrhosis, 9% of early cirrhosis, 40% of Banti's syndrome, 89% of cardiac failure, 50% of acute hepatitis, 1 case (100%) of subacute liver atrophy, 25% of cholecystopathy, 80% of hepatic cancer, 29% of hypertension without failure, 70% of emphysema, 50% of hypothyroidism, 11% of malignancy and 67% of miscellaneous diseases. The cases in which the value of K exceeded the upper limit of the control range were 1 case of early stage of primary biliary liver cirrhosis (100%), 33% of cases with chronic hepatitis and 50% of Hodgkin's disease. Three cases with hyperthyroidism remained within the range of control.

The changes in K value according to the course of the disease were studied on the same patients as illustrated with the arrow in Fig. 5. In the group of cirrhosis, K value decreased in accordance with the appearance of ascites. In one case of Banti's syndrome the value of K decreased after splenectomy. One case of Hodgkin's disease also showed a remarkable decrease in K value after administration of mytomycin.

(5) Hepatic blood flow determination on various diseases

By multiplying K with the blood volume which was determined with T-1824, the liver blood flow per minute was calculated in 40 subjects. Total hepatic blood flow ml./min., the value expressed in body surface and minute ml./M^2/min. (HBF/M^2/min.) and that expressed in body weight and minute ml./Kg./min. (HBF/Kg./min.) will be described in this order.

The values in ten controls ranged from 514 to 962 ml./min. with a mean of 749 ml./min., HBF/M^2/min. varied from 361 to 660 with a mean of 467 ± 80 ml./M^2/min., and HBF/Kg./min. ranged from 10.6 to 20.1 with a mean of 14.4 ml./Kg./min. Eight cirrhotics showed a decreased value of HBF varying from 310 to 552 ml./min. with a mean of 437 ml./min., HBF/M^2/min. ranging from 207 to 346 with a mean of 283 ± 39 ml./M^2/min. And HBF/Kg./min. was between 5.7 and 11.3 with a mean of 8.8 ml./Kg./min. The difference

between these mean values and that found in the control group was noteworthy ($P<0.05$). In cardiac disease, hepatic blood flow was calculated by multiplying K_L with the blood volume. It ranged from 241 to 693 ml./min. with a mean of 532 ml./min., HBF/M²/min. varied from 184 to 534 with a mean of 378 ± 76 ml./M²/min. And HBF/Kg./min. varied from 6.4 to 16.9 with a mean of 12.3 ml./Kg./min. The small difference between this and the control was not significant ($P>0.05$) and many of them were within the normal limit though the difference of K value between cardiac and control was quite marked.

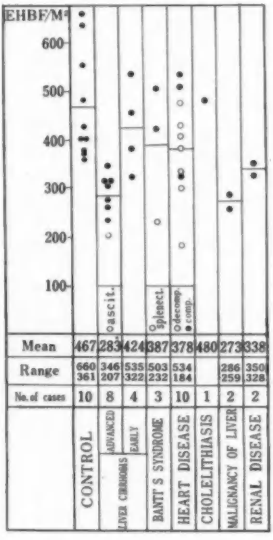

Fig. 6. Hepatic blood flow (ml./M²/min.) in various diseases.

Note: * : Significant difference ($P<0.05$) compared with the mean value of the controls.
ascit. : Cirrhosis with ascites
splenect. : Splenectomized cases with Banti's syndrome
decomp. : Decompensated cardiac disease
comp. : Compensated cardiac disease

(6) Correlation of K value with venous pressure, BSP retention and renal clearance tests

In cardiac disease, the value of K decreased in proportion to the increase in venous pressure, and this correlation was highly significant ($r=-0.94$, $P<0.01$) (Fig. 7).

Although, in general, the value of K showed no correlation with the BSP retention (Fig. 8), the lower was the K, the higher was the BSP retention in cardiac disease with exception of 1 case of advanced hepatic dysfunction (BSP 60%, K 0.154).

As is apparent from Fig. 9, relative correlation was found between K and RBF in nephritis ($r=0.53$, $P=0.05$), but insignificant in the hypertension ($r=-0.32$, $P>0.05$). No correlation was found between K and GFR both in nephritis ($r=+0.48$, $P>0.05$) and in hypertension ($r=-0.22$, $P>0.05$).

(7) Changes in K value caused by rapid transfusion and administration

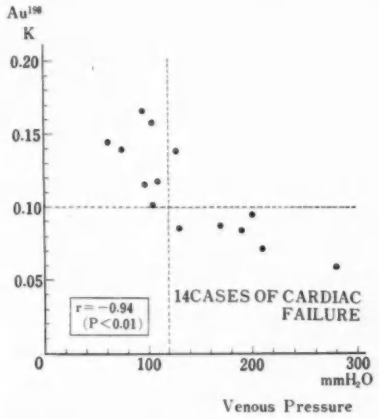

Fig. 7. Correlation between Au^{198} colloid disappearance rate constant (K) and venous pressure in patients with cardiac failure.

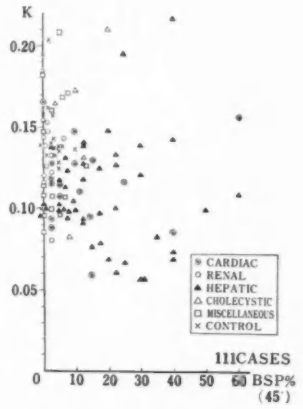

Fig. 8. Changes in disappearance rate constant plotted against BSP retention.

of various drugs

After intravenous administration of colloidal gold, the control values of K were determined from the activity curve during the first 8 to 10 minutes of the experiments. Then this curve was modified by various procedures, namely, rapid infusion of fresh whole blood, plasma or 50% glucose solution, intravenous injection of aminophylline (250 mg.), théraptique (45 mg.) or 10% decholin (40 ml.), intramuscular injection of epinephrine (0.13 mg./Kg.) or gradual intravenous administration of epinephrine or nor-epinephrine (1 mg. was diluted into 300 ml. of physiologic saline solution).

Effect of rapid infusion: Fig. 10 shows infusion speed (ml./min.) on the

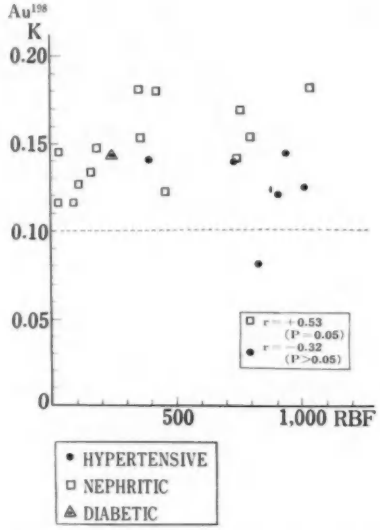

Fig. 9. Correlation between disappearance rate constant (K) and renal blood flow in patients with nephritis, hypertension and Kimmelstiel-Wilson syndrome.

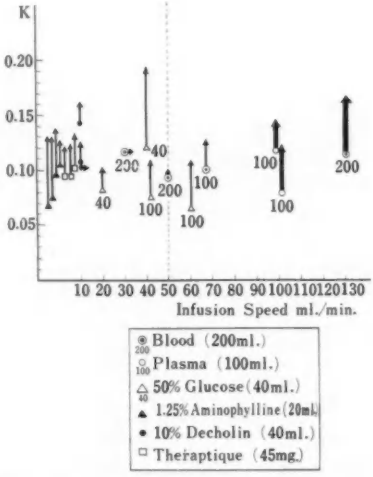

Fig. 10. Increase in disappearance rate constant (K) produced by the infusion of blood, plasma, glucose, aminophylline, decholin and théraptique. The arrows show K-value after the effect of the infusion appeared.

horizontal axis and K value on the vertical axis, and the arrows indicate the K value after the infusion. By rapid infusion of blood or plasma, increases in K run roughly parallel to that of infusion speed, if 50 ml./min. was exceeded.

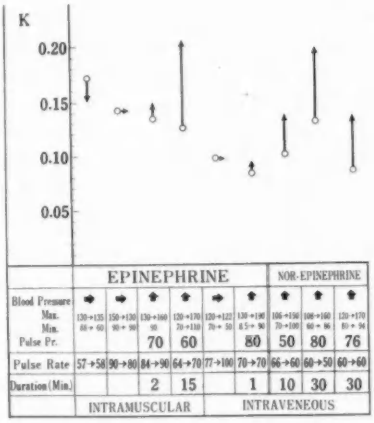

Fig. 11. Changes in disappearance rate constant (K) and the elevation of blood pressure produced by the infusion of epinephrine and nor-epinephrine. The arrows show K-value after the effect of the injection appeared.

On the contrary, 50% glucose resulted in a remarkable increase in K value even when the infusion speed was less than 50 ml./min.

Effect of epinephrine and nor-epinephrine (Fig. 11): Both showed the increase in the K value almost in parallel with the increase in the pulse pressure. In all cases with one exception, changes in pulse rate were not significant.

Effect of various drugs (Fig. 10): In all 4 cases who received aminophylline intravenously, an increase in K value was observed without any changes in blood pressure or pulse rate. In all 3 cases with théraptique infusion the K value increased, while one case was supervened deep respiration at the same time. Two cases of 3 with decholin injection also showed increase in K value.

Influence of neurogenic stimuli: Five cases of rather nervous individual showed a marked increase in K value as a response to pain stimuli which were induced by blood sampling during experimental period (ranged from 1.3 to 3.8 times as compared with the control value) (Table III). In these cases coincidental findings of smaller K values were seen before any stimulation given.

Table III. Changes in Disappearance Rate Constant (K) Produced by Pain-Stimulation

No.	Disease	K_{before}	K_{after}	K_a/K_b
148	Spinal caries	0.124	0.165	1.3
55	Liver cirrhosis	0.056	0.106	1.9
150	Hypertension	0.124	0.315	2.5
81	Liver cirrhosis	0.026	0.090	3.6
83	Hypertension	0.072	0.273	3.8

Discussion

Since the studies by Dobson and others,[1)-7)] the hepatic blood flow is estimated by the disappearance rate constant of colloid at periphery. There have been no extensive studies to reevaluate the accuracy of this method in cases of some circulatory disturbances. Nakanishi[18)] has shown that in cardiac failure, the complete diffusion of T-1824 required 1-2 hours or longer and the ratio of rapid circulating plasma to the total plasma volume decreased to 63-83 per cent while that in normals averaged 91 ± 3 per cent.

In the present study of normal cases without any signs of cardiac failure, an interrelation of $K_H \fallingdotseq K_P \fallingdotseq K_L$ was found. As illustrated schematically in Fig. 2, the injected material can be mixed completely with the circulating blood within the first few minutes. After this period, injected colloid disappears exponentially from the blood (peripheral phase) and accumulates only in the liver (liver phase). Under these circumstances, two equations $C=C_0e^{-kt}$ and $C=C\infty\ (1-e^{-kt})$ must have the theoretically same rate constant K as stated by Dobson[1)] or Siri[8)]. We confirmed this relation to be true in normals and concluded that any of these K could represent the hepatic blood flow.

However, in cases of cardiac failure, the discordance of K values was noted in this study ($K_H > K_P \geqq K_L$). Thus in cardiac failure, the colloidal space of the periphery (over the thigh) cannot be considered equal to that of the heart region. Because in the former, the stasis of the colloid may exist within the slow circulating space of the small vessels, and this could elucidate the finding of $K_H > K_P$ (Fig. 4). In addition to this, blood stasis (depot) can occur at splanchnic area (Fig. 4) which might eliminate the injected material functionally from the rapid circulating blood in parallel with the phagocytosis of the liver. This could explain the relationship of $K_L < K_H$ or K_P. Therefore the peripheral disappearance rate constant (K_P, K_H or Kv) could not represent the true blood flow of the liver when cardiac failure supervened. These constants also reflect the process of prolonged diffusion. In such a case, the use of hepatic accumulation ratio (k_L) would be more reliable for the determination of the hepatic blood flow.

This is also applicable in cases with splenomegaly, especially when complicated by liver cirrhosis, where effective hepatic blood flow decreases markedly. Phagocytic action of spleen would be relatively active and results in the fact that K_P becomes higher than K_L. While in cases with moderate splenomegaly K_P equaled practically to K_L. In these cases, activity curve at the spleen showed a rapid saturation within a few minutes. The value of K was calculated by using a slope after complete mixing, generally within several minutes after injection, so K_P will become equal to K_L in spite of early splenic phagocytosis. In the former instances, splenomegalic cirrhosis, K_L seems to be more reliable representation of the hepatic blood flow.

Comparing the venous sampling method with the external counting method, the disappearance rate constant from the vein (Kv) showed smaller value than that from the external counting method. Since in our series Kv was determined only by using the initial rapidly falling section of the colloidal activity, this difference was about 10% as shown by Dobson.[1] On the other hand, the value of Kv in cardiac failure fell between K_H and K_P, therefore $K_H > Kv > K_P$. Under these circumstances, the venous blood represents the colloidal space between that of the heart region and of the thigh. Higher value was obtained both in Burkle's series by arterial sampling, and in Vetter's series by external determination.

The slow component of the activity curve has been attributed mainly to the remaining of the smaller colloid particles (about 10% of the total injected material), and partly to the stasis of colloid within the slow circulating part of the muscles. When an external counting method is used, an influence of high activity from the liver cannot be excluded. Krook[3] calculated removal percentage by extrapolation to zero time of the initial and terminal components of the disappearance curve, and reported that the removal percentage would be more than 90% in the normal cases. In our series, as shown in Fig. 2, this ranged from 86 to 96%. This difference between Krook's and ours probably comes from the difference in scintillator or collimator used. The activity curve obtained on the heart region showed a relatively higher value of slow component (removal percentage 55–70%). This must have been due to the effect of the high activity in the liver, though a sufficiently collimated and shielded probe was used.

By the determination of K_L, the infinite activity level C_∞ was reached in a relatively short period (20 to 30 min.), therefore registration time could be shortened by this method. However, by K_P determination, longer time (60 min. or more) was needed for the slow component to stabilize.

Administration dosage (μc) of Au^{198} colloid necessary for external determination has been varied by different investigators. For instances, 100 μc was used by Krook, 50–100 μc by Vetter, 15 μc by Burkle and 10 μc by Miwa.[21] In our study an arbitrary dosage of 50 μc was used. This dosage can further be reduced when only determination of K_P or K_L was made, instead of measuring of K_H.

It has been known that the fluctuation of K value occurred frequently when the examination was carried out in different time or day.[6] On successive determinations, a reproducibility of K value was noted by Burkle and Vetter.[4][6] In contrast to the previous works, we demonstrated a good reproducibility in this study even when the result of a month apart was compared.

The method used in this study showed a better reproducibility than the BSP method.[22] This is due to the fact that the method used in the present work studies the liver as a whole in comparison to BSP method which calculates the local function of the liver.[22]

The control value of K is seen in Table 4A comparing with the value of

Table IV. Comparison of Disappearance Rate Constant by the Authors with Those in Previous Reports

A: Control

	Method	Colloid	No. of cases	K
Dobson[1)2)]	Arterial sampling	$CrP^{32}O_4$	29	0.282
Nardi[7)]	Blood sampling	$CrP^{32}O_4$	21	0.336
Vetter[4)5)]	G.M. counter	Au^{198}(H)	25	0.263
Krook[3)]	S. counter	Au^{198}(H)	30	0.158 (0.116~0.197)
Burkle[6)]	S. counter	Au^{198}(O)	22	0.196 (0.154~0.214)
Authors	S. counter (2-channels)	Au^{198}(H)	29	0.146 (0.100~0.203)

B: Cirrhotic

Vetter[4)5)]	ditto	ditto	12	0.095 (0.051~0.143)
Krook[3)]			33	0.092 (0.022~0.178)
Burkle[6)]			11	0.063 (0.029~0.171)
Authors			Advanced 23	0.083 (0.056~0.126)
			Early 11	0.129 (0.102~0.195)

Note: G. M. counter: Geiger-Müller counter
S. counter: Scintillation counter
Au^{198} (H): Hawell made
Au^{198} (O): Oak Ridge made

other investigators. Krook[3)] reported the value almost similar to ours and he also obtained a lower removal rate of the colloid during its first circulation in the liver (40–55%) as compared to that of Vetter's (78–87%). He thought that this might be the factor for lower K value than others. The authors found almost similar low removal percentage (40–50%).

The hepatic blood flow was calculated from the K value multiplied by total blood volume as in other studies. The mean value obtained in 10 controls was 749 ml./min., 467 ml./M^2/min., or 14.4 ml./Kg./min. These values are almost equal to those reported by Krook[3)] (731 ml./min. or 10.4 ml./Kg./min.), but smaller than those reported by Vetter[4)], Burkle[6)] and Nardi.[7)] This difference is due to the difference in K values.

The significance and usefulness of this method is also quite evident in

clinical studies.

As we all know, K value increases proportionally with the volume of effective blood flow in the liver with direct contact to the sinusoid, but decreases with a shunt volume inside or outside of the liver. In cirrhosis, as Table 4B shows, the similar results were obtained by both Vetter and Krook. However, they disagree with the results of Burkles. This difference might be produced by the difference in severity of cirrhosis in each group. In view of this, to obtain an accurate K value our cases were divided into two groups, early and advanced, according to the clinical symptoms and laboratory studies. The difference of K value between these two groups was highly significant as seen in Fig. 5. In advanced cases with a presence of ascites, K value was lower in comparison with that of the same case before the occurrence or after the disappearance of ascites. This is attributed to the effect of the ascitic formation which produces some mechanical pressure upon portal and splanchnic circulation.

The value of K ($K \propto F/V$) is an index derived from a relative magnitude of cardiac output (F) and circulating blood volume (V). In the decompensated state, the K value decreased markedly as was illustrated in Fig. 5 or Fig. 7. This finding is well correlated with previous studies[9)15)] stating that the hepatic blood flow by BSP method decreased almost in parallel with the diminution of cardiac output by Fick method. In cardiac failure, in spite of a significant difference of K value from controls, the hepatic blood flow ($K \times V$) showed little difference (Fig. 5, Fig. 6). This is attributed to the increased circulating blood volume (V), and this indicates the reverse relation between K and the circulating blood volume. In view of these, the decrease in K value in congestive heart failure is thought to be a reflection of the diminution of cardiac output, increase in circulating blood volume, and the disturbance of hepatic out-flow affected by elevated venous pressure. The decrease in K values in congestive failure (Fig. 5) represents the influence of these factors mentioned above, while Fig. 6 shows that the diminution of hepatic blood flow ($K \times V$) in congestive failure is caused mainly by the decreased cardiac output.

Except one case with complicated severe hepatic cell dysfunction, the decrease in K value in congestive failure stood almost in parallel with the increase in BSP retention per cent. However, the diminution of BSP removal rate through liver could hardly be observed by Rapaport and Meyer,[9)15)] though marked decrease in BSP clearance was present in congestive failure. Therefore, an increased BSP retention per cent in congestive failure could reasonably be attributed to decreased hepatic blood flow and partly to supervened hepatic cell dysfunction.

It is also considered that hepatic or splenic phagocytic function might have some influence on K values, and that after the colloidal saturation in the reticulo-endothelial system, the K value again shows some decrease. In cirrhotic liver, Kupffer cell function is supposed to be very active independent of the disturbed function of hepatic cell. This is the reason why hepatic blood flow

in cirrhosis can be estimated by the Au^{198} colloid which is taken up by Kupffer cell. A high K value was also seen in chronic hepatitis in spite of increased BSP retention rate (20%, 0.148; 40%, 0.216). A marked decrease in K value is noted in acute hepatitis (40%, 0.071). In primary biliary cirrhosis, it decreased from 0.195 to 0.125 with the appearance of jaundice and in Hodgkin's disease it decreased from 0.209 to 0.123 after the administration of mytomycin. In these diseases, a decreased Kupffer cell function may present and this may resulte in a low K value. Burkle[6] also noted decreased K values in his study of 11 cases with acute hepatitis. Thus the value of K could not represent the true hepatic blood flow in such an instance. On the contrary, high value of K was observed in Hodgkin's disease before the treatment with mytomycin (0.209), in chronic hepatitis (0.216) and in primary biliary liver cirrhosis (0.195) where an increase in Kupffer cell number was observed pathologically. It is therefore probable to assume that removal rate of colloid might be accelerated by increased number of Kupffer cells.

The results obtained in 3 cases of hyperthyroidism (B.M.R. +48%, +34% and +17%) were noteworthy. Despite the fact that hyperthyroidism should have an increased cardiac output, the K value fell within normal range. Meyer[10] found that an increased output (Fick method) in thyrotoxicosis did not result in an increase in liver blood flow (BSP method), and assumed that by-path of the liver may be its reason. Our results agreed with his findings.

As is apparent from Fig. 16, the K values of nephritic cases were within the control limit. Imura[19] reported negative correlation between K and renal blood flow (RBF), indicating the compensatory mechanism of the liver, however, this was not seen in our study.

To clarify the relation of cardiac output to the disappearance rate constant (K), rapid transfusion of fresh whole blood or plasma was performed, inducing an augmented venous return. Cardiac output had been reported[14][17] to be increased by this procedure. In our study, an increase in K was also observed in parallel with the rate of infusion but not with total volume of infusion (Fig. 10).

The elevated blood pressure and increased pulse pressure caused by epinephrine or nor-epinephrine demonstrated an increase in the K value. As has been shown by many investigators,[16] cardiac output is closely related to the magnitude of the pulse pressure multiplied by heart rate. With a fairly constant heart rate in our study, the pulse pressure appeared to play an important role in the increase in cardiac output, thus resulting in the increased K value. Moreover, by many authors[1][11][12][23] epinephrine and nor-epinephrine were reported to affect hepatic blood flow not only by the effect upon the systemic circulation but also by the direct effect upon hepatic or splanchnic vascular bed per se. However, the mechanism of the latter could not be proved by the present method.

The administration of aminophylline also showed an increased K value in 4 control cases and this may be explained by increased cardiac output.[13]

The mechanism of the effect of théraptique upon liver circulation is not so clear. Probably epinephrine would be excreted from the stimulated adrenal gland, while deep respiration accelarated the venous return from the splanchnic area. This drug induced high K value in 3 controls.

Administration of 50% glucose solution with rather slow infusion showed high K values in 4 control cases. This is probably due to the mobilization of water into vessels from extravascular tissue, thus inducing increased venous return. On the other hand, as shown by Wakin *et al.*,[24] a direct effect upon sinusoid must be taken into account.

Psychogenic effect of pain during the collection of blood samples caused an increased K value. However, its nature is still questioned. The basal K value of the same patient before the needle sticking was so low that it might be possible to assume that the large resting portion of sinusoid was opened and that the passage of the blood through it was resumed which resulted in higher K value than control.

In conclusion, the disappearance rate constant (K) with colloidal gold method reflects not only vascular changes of the liver per se but also the hemodynamics of the whole body.

Summary and Conclusion

(1) A simple new recording apparatus for R.I. was deviced and its usefulness was discussed.

(2) Using this apparatus, hepatic blood flow was determined in 152 cases by Au^{198} colloid method.

(3) Simultaneous determinations of Au^{198} disappearance rate constant at periphery (K_P and K_H) and accumulation rate constant in the liver (K_L) were made in various diseases, such as liver cirrhosis and congestive heart failure etc.

(4) Similar examination is also made after rapid blood transfusion or administration of various drugs, including epinephrine, nore-pinephrine etc.

(5) The K value decreased in congestive heart failure and liver cirrhosis. An increase in the K value was observed in accordance with an increased cardiac output.

(6) An advantage of this method and its clinical significance were discussed.

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Studies on the Expired Alveolar Carbon Dioxide Tension in Chronic Pulmonary Emphysema with Special Reference to Pulmonary Arterial Hypertension

Atsushi SAKAMOTO, M.D. *and* Makoto MURAO, M.D.*

A total number of 68 cases were examined in the present study. Continuous analysis of expired alveolar CO_2 tension, using a rapid infrared meter, was made in 10 normal subjects and 20 patients with chronic pulmonary diseases. In 17 patients, an arterial blood was sampled simultaneously, while alveolar CO_2 tension was analyzed during quiet breathing. This allowed to make a direct comparison between blood and gas tensions. Cardiac catheterization was carried out in 38 patients with emphysema, and the mixed venous CO_2 tension and mean pulmonary artery pressure were measured. The mean pulmonary artery pressure exceeded 18 mm. Hg in 23 of 38 patients, and in all patients with a mixed venous CO_2 tension of more than 55 mm. Hg. The mixed venous CO_2 tension exceeded 50 mm. Hg in 23 of 38 patients, and the correlation between mixed venous CO_2 tension and pulmonary artery pressure was highly significant in these 23 patients ($R=+0.84$). These results indicate that the severity of pulmonary hypertension may be estimated by the expired alveolar CO_2 tension in patients with a mixed venous CO_2 tension of more than 55 mm. Hg.

WITH the recent availability of rapid CO_2 analyzers, DuBois and Fowler have explored a new field in continuous analysis of expired CO_2 tension for estimation of various values pertaining to mixed venous CO_2 tension, arterial CO_2 tension, uneven ventilation-perfusion relationship, ratio of pulmonary blood flow per equivalent lung volume, and also cardiac output.[1)-5)] These values are really essential in evaluating the respiratory insufficiency and pulmonary circulatory disturbance in patients with chronic pulmonary diseases,[6)] and it seems very convenient for the clinical application that the values are obtained without hazardous procedures such as arterial puncture or cardiac catheterization. In this paper, an attempt has been made on normal subjects and patients with chronic pulmonary emphysema to reevaluate the continuous analysis of expired CO_2 tension following the method of Silvertson and Fowler, and clinical applicability of the methods is also discussed.

Materials and Methods

Ten normal individuals were studied for the control, of whom 8 were men and 2

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were women, ranging in age from 19 to 38 years. Twenty patients with chronic pulmonary diseases were also studied, 10 of whom had pulmonary emphysema, ranging in age from 41 to 67 years, with an average of 55 years. The other 10 cases of chronic pulmonary diseases included 4 cases of bronchial asthma, 2 cases of pulmonary fibrosis, 2 cases of chronic bronchitis, and one case each of beryllium poisoning and bronchiectasis.

The method used in this tudy was smilar to that originally described by Sivertson and Fowler.[4] The infrared CO_2 meter* and its standard cell, through which the subject breathed, was set up as such that the distal end of the sampling tube of the CO_2 meter was connected to a prime mover of pneumotachograph. The prime mover was a Lilly type, which had an internal volume of 70 ml., and a flow resistance of 1.15 cm. H_2O per liter per second. The total volume of dead space was no more than 150 ml. The pick-up system of the prime mover was a type of wire resistance strain gauge differential manometer.** A warm-up period of 2 hours or more provided sufficient stability for sensitivity of the instruments. Then the infrared CO_2 analyzer was calibrated with mixtures of CO_2 in room air, which had been previously analyzed with a Scholander's apparatus. Dry gas concentrations were changed to tension by multiplying with the barometric pressure corrected for water vapor tension at body temperature. Calibrations were made before and after each test, and over-all accuracy of CO_2 tension described below was considered to be ± 1 mm. Hg. The CO_2 detector system was capable of 100% response in a 0.05 second and 0.2 second, when the rate of air flow was 500 ml. per second and 100 ml. per second respectively. Both CO_2 tension and ventilatory volume were recorded with an ink-writing oscillograph*** at a paper speed of 6 or 10 mm. per second. The area of the flow tracing, as it was deflected from zero line by each breath, was converted into a volume by planimetry or by counting squares. All volumes were corrected to BTPS.

Wearing a nose clip, subjects sat in chairs during a suitable rest period. Then they breathed room air through a mouth-piece attached to the sampling tube. CO_2 and tidal volumes were recorded for several natural breaths and for a forced maximal expiration following normal inspiration (Fig. 1). Recordings were made for a maximal expiration following breathholding at the inspiratory level of the normal ending (Fig. 2). The period of breathholding was intended to be 25 seconds or longer, as could be tolerated. All the procedure mentioned above was repeated and recorded. Then recordings were also made before and during 30 seconds of voluntary hyperventilation terminated by a forced maximal expiration (Fig. 3). For hyperventilation, subjects were directed to take approximately 12 breaths in 30 seconds.

Thirty-eight patients with chronic pulmonary emphysema were studied by right heart catheterization, and the partial pressure of CO_2 in the mixed venous blood and the mean pulmonary artery pressure were measured.[7] In 17 patients, an indwelling needle was inserted into the brachial artery and arterial blood was sampled, while the expired alveolar gas was analyzed continuously during natural breathing. The whole blood was analyzed for CO_2 and O_2 by the method of Van Slyke and Neill.

* Liston-Becker Model 16 Beckman Co.

** Toyosokki Co. DLPU-0.03.

*** Nihonkoden Co. W 1–40.

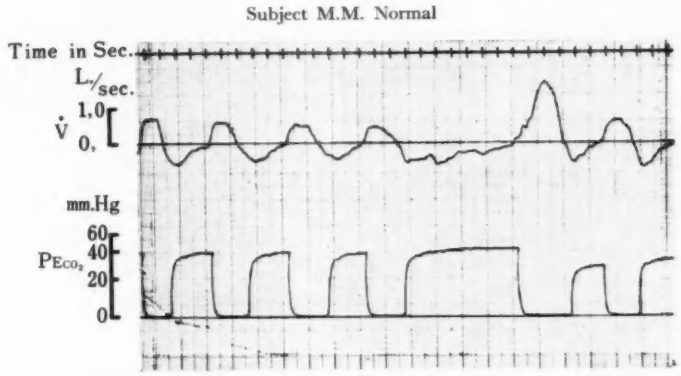

Fig. 1. Record of expired CO_2 tension analysis during normal respiration and forced expiration.

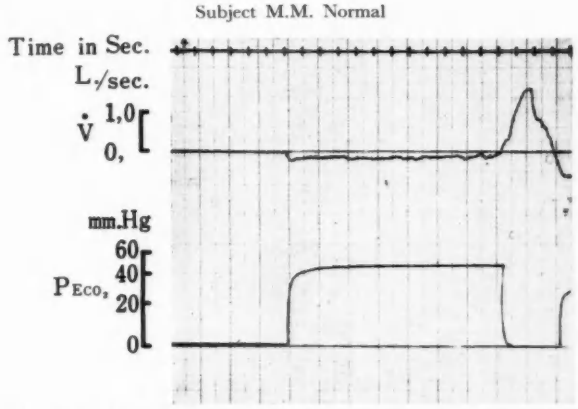

Fig. 2. Estimation of $P\bar{V}_{CO_2}$ by the CO_2 tension curve during forced expiration after breathholding (19 sec.).

The pH was determined with Cambridge pH meter* and the packed cell volume by the method of Wintrobe. The CO_2 tension of blood was determined from the nomogram of Singer and Hastings.[8]

Results

Data of routine pulmonary function tests and that of CO_2 tension which represent the maximal value for any single expiration are summarized in Table I.

Results in Normal Subjects—

The largest variations in end-tidal CO_2 tension during a 45 second-

* 4427 Cambridge pH meter, portable pattern.

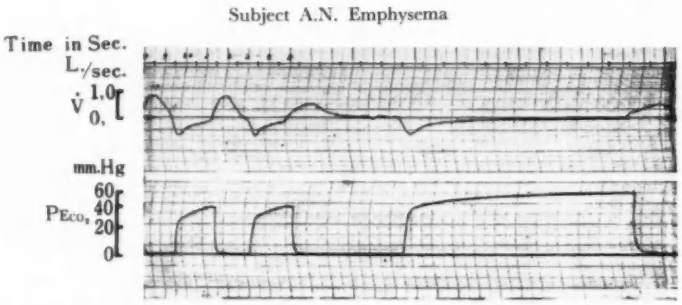

Fig. 3. Record of expired CO_2 tension analysis during hyperventilation and terminal forced expiration.

period in 10 normal subjects were ranging from 1.0–3.0 mm.Hg. During quiet breathing prior to a forced expiration, there was a plateau observed at each end-expiration (Fig. 1). The mean of average end-tidal values for each subject was 38.5 mm.Hg. At the end of normal inspiration following quiet breathing, the breathing was held for an average of 23 seconds. In this case, the alveolar plateau by succeeding forced expiration was essentially horizontal during an expiration of a liter or more for several seconds (Fig. 2). As mixed venous CO_2 tension has been essentially unchanged for 23 seconds or more in these cases, the maximal values of CO_2 tension of maximal expiration after the breathholding were considered to represent the mixed venous CO_2 tension (oxygenated).[4] The average value of estimated mixed venous CO_2 tensions was 45.7 mm.Hg in normal subjects. With maximal expiration following natural breathing, there always occurred slight increase in CO_2 tension (Fig. 1), reaching an average value of 41.8 mm.Hg, at the average value of 2,050 ml. of expired volume (Table I). Assuming that the observed rate of increase in expired alveolar CO_2 tension is equal to that of alveolar CO_2 tension, after about 500 ml. of gas was expired and anatomic dead space was washed out, Fick's principle may be applied to the observed rate of increase in expired alveolar CO_2 tension as a function of time. This expression was shown in the papers of DuBois and Fowler as follows[4][9]:

$$\frac{\Delta P_{ACO_2}}{\Delta t} = \frac{(P\bar{v}_{CO_2} - P_{ACO_2})(\text{diss. slop})\,\dot{Q}\,(P_B - 47)}{ELV} \qquad (1)$$

P_{ACO_2}: partial pressure of CO_2 in the alveolar gas at given time.

$P\bar{v}_{CO_2}$: partial pressure of CO_2 in the mixed venous blood, oxygenated.

diss. slope: the mean slope of the dissociation curve for CO_2 and oxygenated whole blood, normally about 0.46 volume per cent per mm.Hg.

$\dot{Q}$: rate of alveolar blood flow.

P_B : barometric pressure, expressed in mm.Hg (760 ± 8 mm.Hg in Tokyo, Japan).

Table I. Characteristics of Several Types of Breathing

	Normal			Chronic pulmonary diseases					
				Emphysema			Miscellaneous		
	No.	Mean	Range	No.	Mean	Range	No.	Mean	Range
Rest	10			10			10		
V_T (ml.)		570	380～ 850		500	300～ 750		580	330～ 790
$\dot{V}$ (L./min.)		9.0	5.3～13.5		9.0	5.9～15.0		10.2	8.4～13.3
f (resp./min.)		16	9～ 19		18	13～ 22		18	11～ 30
Max. P_{CO_2}(mm.Hg)		38.5	35～ 44		39.0	31～ 48		35.9	29～ 43
Max. expiration									
Vol. (ml.)		2,050	1,060～2,870		1,340	740～2,480		1,890	1,320～2,410
Dur. (sec.)		7.7	3.4～11.5		9.9	5.5～17.6		9.3	3.2～13.8
Max. P_{CO_2}(mm.Hg)		41.8	36～ 46		52.9	45～ 67		44.2	35～ 50
Hyperventilation	10			10			10		
P_{CO_2} before HV (mm.Hg)		37.1	31～ 43		38.5	33～ 44		34.4	30～ 40
Dur. (sec.)		29	27～ 32		30	25～ 37		31	28～ 35
V_T (ml.)		1,840	1,150～3,120		780	460～1,690		1,580	840～3,220
$\dot{V}$ (L./min.)		43	23～ 77		18	10～ 47		31	16～ 55
f (resp./min.)		23	18～ 33		23	13～ 36		21	13～ 40
Max. P_{CO_2} (lowest 3 end-tidal)		20.8	17～ 26		31.9	24～ 38		24.6	20～ 28
Max. expiration after HV									
Vol. (ml.)		3,210	2,000～5,230		1,600	820～3,380		2,340	1,470～3,140
Dur. (sec.)		4.9	2.6～ 7.8		10.0	3.4～11.3		8.7	4.7～16.9
Max. P_{CO_2}(mm.Hg)		26.3	20～ 35		46.5	37～ 58		33.2	25～ 43
Breathholding	10			10			10		
Dur. BH. (sec.)		23	17～ 36	9	19	12～ 27		22	14～ 27
Max. exp. after BH									
Vol. (ml.)		1,880	1,220～2,520	10	1,270	690～1,950		1,740	1,120～2,400
Dur. (sec.)		6.1	2.7～12.0		7.8	3.3～17.5		6.4	3.9～16.0
Max. P_{CO_2}(mm.Hg.)		45.7	41～ 51		55.6	48～ 66		48.1	40～ 52
RV/TLC (%)	8	23	19～ 28	10	61	52～ 68	9	38	24～ 48
MBC (L./min.)		126	89～ 166	9	33	16～ 79		56	27～ 107
MBC (% of predicted)			>100		43	26～ 72		57	33～ 95
MMF (L./sec.)		4.1	2.6～ 5.9		0.50	0.18～1.22		1.37	0.28～ 4.2
Sao_2 (%)					91	75～ 98		96	93～ 100
pHa				8	7.38	7.33～7.46		7.42	7.38～7.46
$Paco_2$ (mm.Hg)					49.3	39～ 62		39.3	35～ 44

Note: CO_2 tensions are maximal values of any single expiration.

V_T	:	Tidal volume	MBC	:	Maximal breathing capacity
$\dot{V}$	:	Minute volume	MMF	:	Maximal midexpiratory flow
f	:	Respiratory frequency	Sao_2	:	Arterial blood oxygen saturation
RV	:	Residual volume	pHa	:	Arterial blood pH
TLC	:	Total lung capacity	$Paco_2$	:	Arterial carbon dioxide tension

ELV : ' Equivalent lung volume for CO_2 at a given time ' includes the capacity of the alveolar gas, pulmonary capillary blood and tissue for CO_2.

The integrated form of the equation (1) is:

$$P_{ACO_2}=P\bar{v}_{CO_2}-(P\bar{v}_{CO_2}-P_{AoCO_2})\ e^{-kt} \qquad (2)$$

P_{AoCO_2}: the value of P_{ACO_2} at zero time.

$$k=\frac{(\text{diss. slope})\ \dot{Q}\ (P_B-47)}{ELV}$$

The difference between the mixed venous tension and the successive alveolar tension was measured on several points of each record of maximal expirations and the logarithm of the difference was plotted against the time from the onset of expiration, as illustrated in Fig. 4. As seen in Fig. 5,

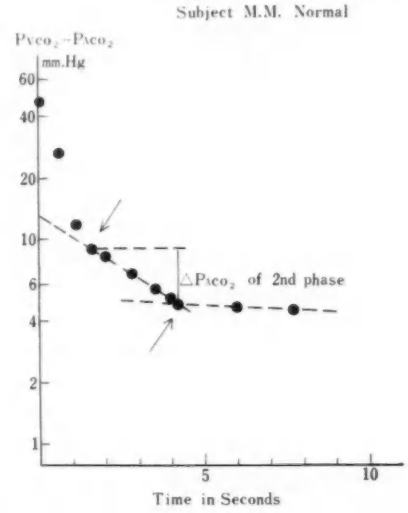

Fig. 4. Mixed venous-alveolar CO_2 tension gradient during forced expiration on the record shown in Fig. 1. The arrows show the points of the initial alveolar CO_2 tension of 2nd and 3rd phase. Estimation of $P\bar{v}_{CO_2}$ is based on the breath-holding method shown in Fig. 2.

we divided each record of forced expirations into three phases. After an average value of 480 ml. had been expired (designated as ' 1st phase '), the rate of decrease (per cent per second) in the tension difference, $P\bar{v}_{CO_2}-P_{ACO_2}$, became constant for the period during which an average of 1,030 ml. was expired (designated as ' 2nd phase '). In Fig. 6, the mean rate of increase in expired alveolar CO_2 tension in the 2nd phase ($\Delta P_{ACO_2}/\Delta t$) was plotted against each initial gradient, which represented the difference at the initial P_{ACO_2} in the 2nd phase ($P\bar{v}_{CO_2}$−initial P_{ACO_2}). In this Fig. 6, the percentage rate of change in the initial gradient was represented by the angle of the straight line connected with the zero point. The average value of $\dot{Q}$/ELV was calculated from the mean percentage rate of decrease for each group by substitution in the equation (1), and these values were shown in Table II. In normal subjects, the mean rate of increase in P_{ACO_2} in the 2nd phase had an average value of 11 mm.Hg and decreased about 21 per cent per second. It was corresponding to an average value of 3.8 liters blood flow per minute per liter of lung volume (Table II). The upward slope of the alvolar plateau decreased progressively toward the end of forced expirations. In the 3rd phase, the

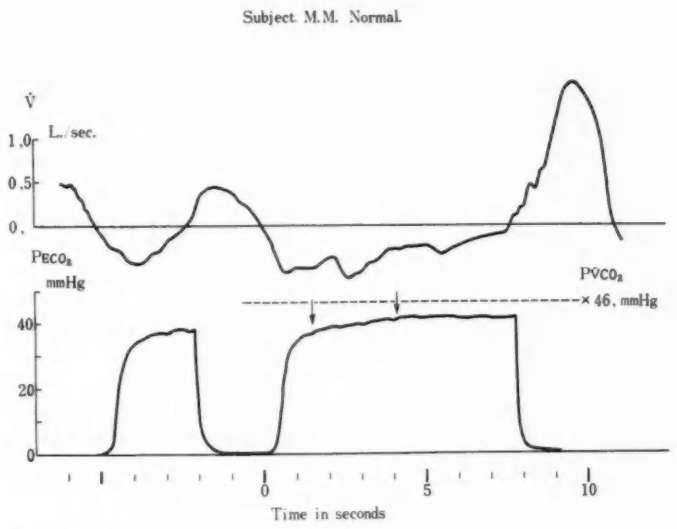

Fig. 5. CO_2 tension curve during normal and forced expiration on the record shown in Fig. 1. The arrows show the same points indicating the initial alveolar CO_2 tension in Fig. 4.

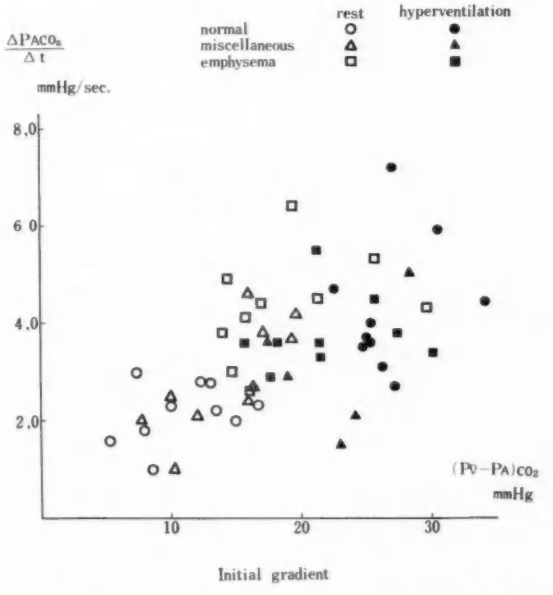

Fig. 6. Correlation between mean rate of increase in alveolar CO_2 tension and mixed venous-initial alveolar CO_2 tension gradient in the 2nd phase.

plateau was almost horizontal, although it showed small variations (Fig. 5). As noted by the more horizontal course of the last three points of Fig. 4, semilogarithmic plots of $P_{\bar{v}CO_2}-P_{ACO_2}$ showed that the percentage rate of decrease became less in the 3rd phase. Similar analyses were made for maximal expirations following hyperventilation (Fig. 7).

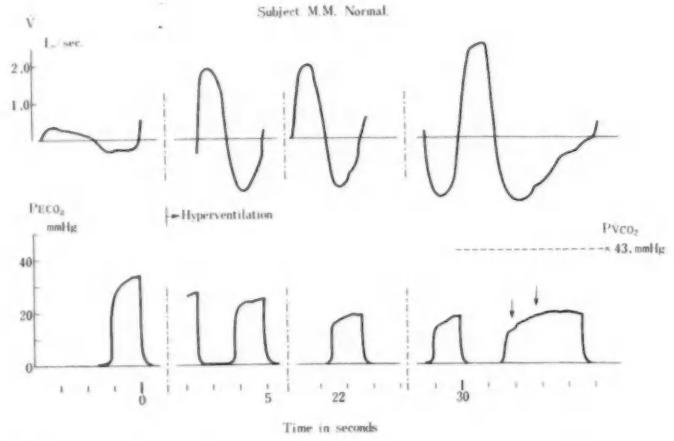

Fig. 7. CO_2 tension during hyperventilation and terminal forced expiration. The arrows show the points indicating the initial alveolar CO_2 tension.

With voluntary hyperventilation, 10 normal subjects increased their minute volume to an average value of 43 liters per minute, as such of 4.8 times at rest. During hyperventilation, end-tidal values of P_{ACO_2} decreased for the first several breaths and then decreased little as long as the respiratory rate was similar. The mean value for the average P_{ACO_2} of the lowest three expirations for each subject was 20.8 mm.Hg, as presented in Table I. On the succeeding forced expiration, maximal CO_2 tension had an average value of 26.3 mm.Hg, at average expired volume of 3,210 ml. during the period of 4.9 seconds. In some records of some cases, maximal values of expired CO_2 tension were observed prior to the end of expiration (Fig. 7). The semilogarithmic plots of $P_{\bar{v}CO_2}-P_{ACO_2}$ showed a period of constant percentage rate of decrease, during which an average 2,100 ml. of gas was expired (2nd phase). With hyperventilation, the values of the initial gradient and mean rate of change in P_{ACO_2} increased in the 2nd phase, but the percentage rate of change was about—18 per cent per second (Table II). Average values of durations were shortened in three phases.

Results in Chronic Pulmonary Diseases—

After comprehensive case history and pulmonary function tests including

Table II. Average Values of Volume, Time, and Changes in CO_2 Tension During Expiration.

Type of expiration	Normal				Chronic pulmonary diseases					
	Max. expiration after normal respiration		Max. expiration after hyperventilation		Max. exp. after norm. respiration				Max. exp. after HV	
					Emphysema		Miscellaneous		Emphysema	
Tot. expiration volume (ml.)	2,040 (1,060~2,870)		3,210 (2,000~5,230)		1,340 (240~2,480)		1,870 (1,320~2,410)		1,610 (820~3,380)	
Vol. of 1st phase (ml.)	480 (260~ 730)		500 (200~ 900)		470 (240~ 780)		520 (250~1,100)		590 (290~1,430)	
Alveolar gas	2nd (10)	3rd (9)	2nd (10)	3rd (9)	2nd (10)	3rd (9)	2nd (10)	3rd (10)	2nd (9)	3rd (9)
Volume (ml.)	1,030 (360~1,440)	520 (130~1,070)	2,100 (1,190~3,280)	610 (250~1,460)	440 (190~660)	440 (160~1,040)	870 (480~1,330)	490 (180~1,100)	590 (190~1,150)	440 (100~890)
Duration (sec.)	2.3 (0.5~3.7)	4.5 (0.5~7.5)	1.7 (0,4~3.2)	2.6 (1.2~4.4)	2.4 (1.1~3.6)	6.2 (3.0~13.8)	2.4 (1.4~4.1)	4.7 (1.3~ 10)	2.4 (1.5~3.2)	6.2 (4.0~7.4)
Mean rate of increase (mm.Hg/sec.)	2.2 (1.0~3.0)	0.4 (0. ~1.0)	4.3 (2.7~7.2)	1.1 (0.3~2.5)	4.3 (2.6~6.4)	1.0 (0.7~1.6)	2.9 (1.0~4.6)	0.6 (0. ~1.0)	3.8 (2.1~5.5)	0.9 (0.3~1.3)
Initial P_{ACO_2} (mm.Hg)	36 (33~ 38)	39 (36~ 43)	17 (14~ 22)	24 (18~ 29)	38 (31~ 44)	48 (38~ 58)	34 (30~ 42)	41 (32~ 48)	33 (23~ 43)	41 (30~ 50)
Init. gradient, $P\bar{v}$-P_A (mm.Hg)	11.0 (5~ 15)	6.4 (3~ 9)	26.8 (23~ 34)	20.4 (16~ 25)	18.8 (14~ 30)	8.6 (6~ 14)	14.4 (8~ 20)	7.7 (2~ 14)	22.1 (16~ 30)	13.6 (6~ 23)
Change in $P\bar{v}$-P_A (% per sec.)	-21 (-12~-41)	-5 (0~-13)	-18 (-10~-27)	-5 (-1~-13)	-24 (-15~-34)	-11 (-6~-16)	-20 (-10~-29)	-7 (0~-11)	-18 (-11~-25)	-7 (-3~-11)
Calc. $\frac{\dot{Q}}{ELV}\left(\frac{L./min.}{L.}\right)$	3.8	0.9	3.3	0.9	4.4	2.1	3.7	1.3	3.3	1.4

Note: Number of persons in parentheses in column headings. Range of values in parenthesis in table. One normal and one patient showed no change of rate in late expiration.

fluoroscopic examination, 20 patients were divided into 2 groups which consisted of 10 typical pulmonary emphysema and 10 cases with other forms of pulmonary disease. Data listed in Table I indicate that pulmonary insufficiency is compensated better by hyperventilation in the miscellaneous group than in the emphysema group at rest. In these patients, the breath-to-breath variation in resting end-tidal P_{ACO_2} was greater than that of normal subjects, ranging from 1.3–4.8 mm.Hg during a 45-second period. In many cases of pulmonary disease, resting end-tidal P_{ACO_2} was frequently less than normal. However, with a forced expiration, an increase in P_{ACO_2} of about 10 mm.Hg was observed, reaching average values of 52.9 and 44.2 mm.Hg in emphysema group and others respectively. In patients with emphysema listed in Table I, maximal expirations following natural breathing were prolonged (an average value of 9.9 seconds of duration) and the expired volumes were smaller (an average value of 1,340 ml.) than normal. Nine of 10 patients with emphysema held their breath for 12 to 27 seconds, averaging 19 seconds. The alveolar plateau of maximal expirations after breath-holding was essentially horizontal during an expiration of the last 0.8 liter during several seconds (Fig. 8). In these patients, as well as in normal sub-

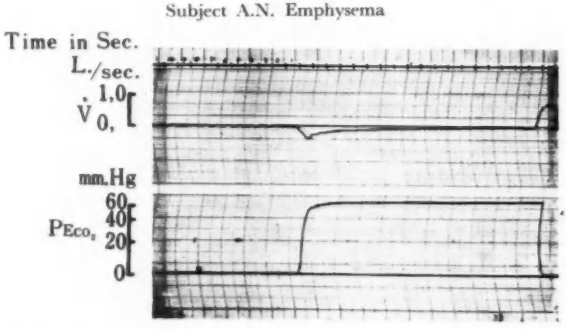

Fig. 8. Estimation of $P_{\bar{V}CO_2}$ by the CO_2 tension curve during forced expiration after breathholding (21 sec.).

jects, the maximal values of these alveolar plateau tensions appeared to represent $P_{\bar{V}CO_2}$, averaging 55.6 mm.Hg (Table I). The semilogarithmic plots were made for maximal expirations and they also showed a constant percentage rate of decrease in the 2nd phase, during which an average 440 ml. of gas was expired (Fig. 9). In cases of emphysema, the mean rate of increase in P_{ACO_2} in 2nd phase had an average value of 4.3 mm.Hg per second, which was equal to that observed in normal subjects in the 2nd phase of maximal expiration following hyperventilation. The relatively large average value of 18 mm.Hg of initial gradient was observed, and it decreased at the rate of about 24 per cent per second. In the 3rd phase, the mean rate of increase in P_{ACO_2} had an average value of 1.0 mm.Hg per second, which was similar to that

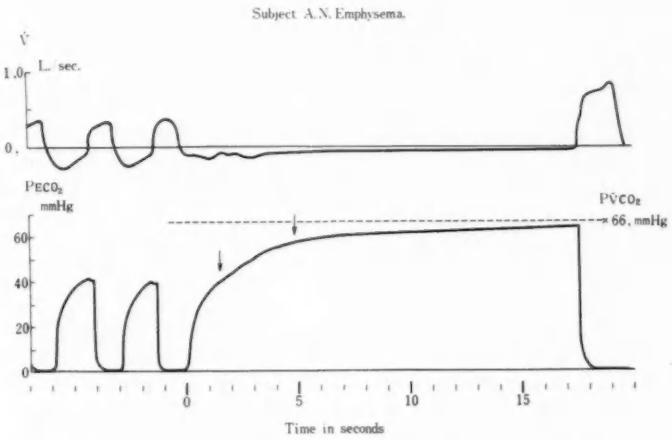

Fig. 9. CO_2 tension curve during nomal and forced expiration. Estimation of $P\bar{V}CO_2$ is based on the breathholding method shown in Fig. 8. Arrows show the points of the initial alveolar CO_2 tension.

value observed in normal subjects in the same 3rd phase of the maximal expiration following hyperventilation (Table II).

The patients with emphysema showed less response to voluntary hyperventilation than normal subjects and their average minute value was 18 liters per minute. As the reductions of end-tidal values did not exceed several mm.Hg during hyperventilation, it appeared that an effective alveolar ventilation of emphysematous lungs could not be increased voluntarily. With the succeeding forced expiration, the increase in the expired volumes was smaller in patients with emphysema than in normal subjects. The maximal P_{ACO_2} of the succeeding forced expiration, with a mean of 46.5 mm.Hg, exceeded the resting end-tidal value in all cases. These expirations were plotted semilogarithmically and divided into three phases (Fig. 10). In many cases of emphysema, the maximal value of expiratory flow rate of each forced expiration was observed within the 1st phase (Fig. 11). In the 2nd phase of maximal expiration following hyperventilation, an average value of 590 ml. for the expired volume was obtained, and the increase in expired volumes was far less than normal. An average duration remained unchanged throughout three phases, after hyperventilation. The mean rate of increase in P_{ACO_2} in the 2nd phase had an average value of 3.8 mm.Hg per second, which was similar to those observed during a forced expiration after natural breathing. The initial gradient was slightly increased, averaging 22.1 mm.Hg. This resulted in the value of about -18 per cent per second for the calculated percentage rate of decrease (Table II). Ten patients with miscellaneous pulmonary diseases showed intermediate values of the gradient and its rate of change.

Increase in alveolar CO_2 tension (ΔP_{ACO_2}) and volume of expired alveolar

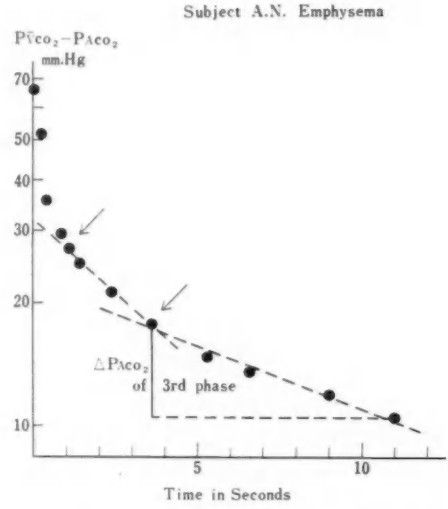

Fig. 10. Mixed venous-alveolar CO_2 tension gradient during forced expiration on the record shown in Fig. 3. Estimation of $P\bar{v}_{CO_2}$ is based on the breathholding method shown in Fig. 8. Arrows show the points of the initial alveolar CO_2 tension of 2nd and 3rd phase.

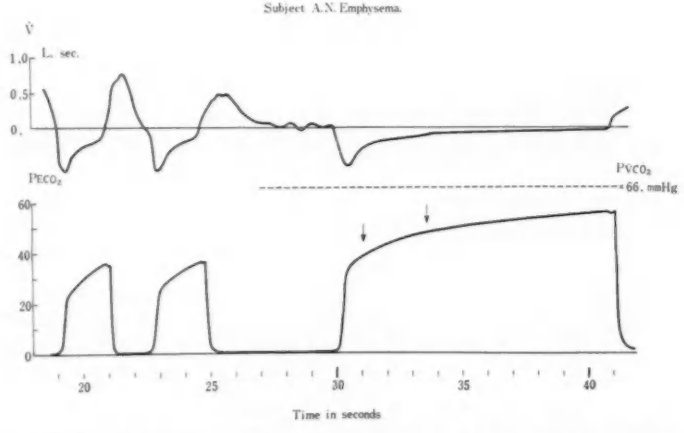

Fig. 11. CO_2 tension curve during hyperventilation and terminal forced expiration on the record shown in Fig. 3. The arrows show the same points indicating the initial alveolar CO_2 tension in Fig. 10.

gas in the 2nd phase of maximal expiration were plotted in Fig. 12. In patients with emphysema, the differences from normal findings were larger ΔP_{ACO_2} and smaller volumes of expired alveolar gas. These 2 components

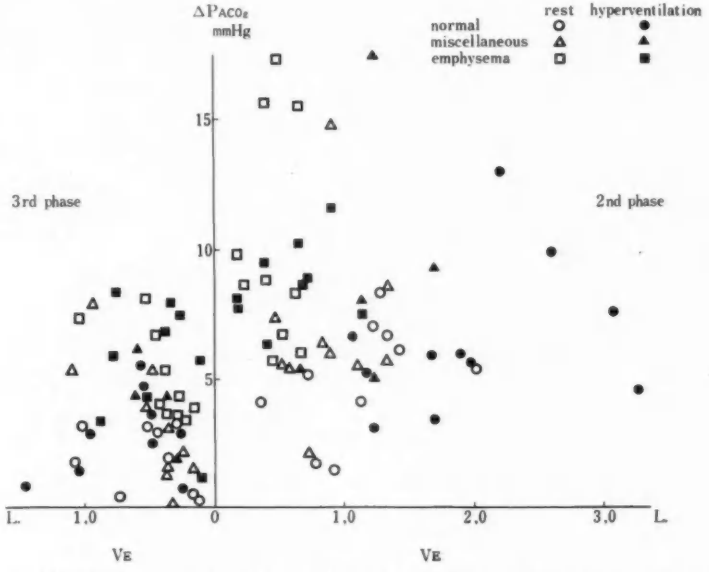

Fig. 12. Increase in alveolar CO_2 tension plotted against volume of expired alveolar gas (2nd and 3rd phase).

were divided by a duration of the 2nd phase for each subject, and a correlation between the mean rate of increase in alveolar CO_2 tension ($\Delta P_{ACO_2}/\Delta t$) and mean rate of air flow in the 2nd phase was obtained (Fig. 13). As shown in Fig. 13, $\Delta P_{ACO_2}/\Delta t$ and the mean rate of air flow increased in normal subjects after hyperventilation, but did not increase in patients with emphysema. As plotted in Fig. 14, a significant correlation between $P_{\bar{v}CO_2}$ and mean pulmonary artery pressure was observed in 38 patients with emphysema ($R=+0.67$). The mean pulmonary artery pressure exceeded 18 mm.Hg in 23 of 38 patients, and in all patients with a $P_{\bar{v}CO_2}$ of more than 55 mm.Hg. The $P_{\bar{v}CO_2}$ exceeded 50 mm.Hg in 23 of 38 patients, and the correlation between $P_{\bar{v}CO_2}$ and pulmonary artery pressure was highly significant in these 23 patients ($R=+0.84$).

Discussion

In general, the difficulty of forced expiration in patients with emphysema is due to the check valve mechanism.[10] This is well demonstrated by the fact that a forced expiration shows a peaking of expiratory flow early in expiration, followed by a rapid decrease to the lower rate of flow, namely the 'leakage flow'. By a forced maximal expiration after deep inspiration, these characteristics of the pattern of expiratory flow were distinguished in patients with emphysema (Fig. 11). In normal subjects it has been known that the rate of

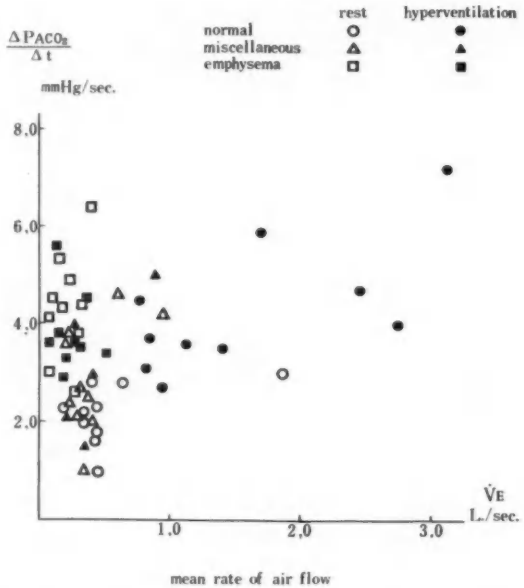

Fig. 13. Mean rate of increase in alveolar CO_2 tension plotted against mean rate of air flow in the 2nd phase.

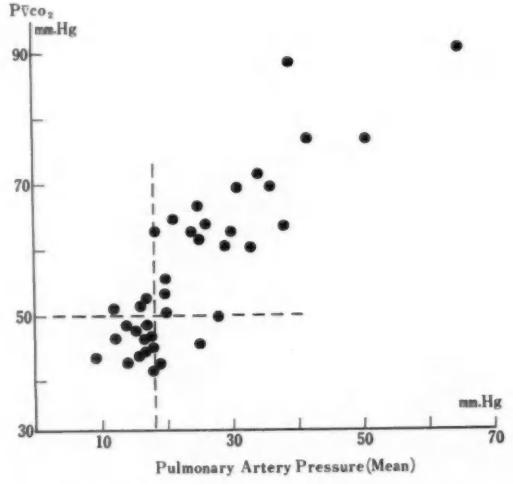

Fig. 14. Correlation between mixed venous CO_2 tension and pulmonary artery pressure (Mean) in the patients with pulmonary emphysema. Values shown in this figure are measured by catheterization technics.

air flow of forced expiration decreases progressively after peak flow, but that a fairly large rate of flow is maintained for the major part (Fig. 7).[11] In normal subjects the initial alveolar gas of the 2nd phase was always delivered on the ascending stage of the peak flow. On the contrary, in many patients with emphysema, the initial alveolar gas of the 2nd phase was delivered with suggestive POC (Point Of Closure by check valve mechanism) after the peak flow (Fig. 11). This accounts for the results that the mean rate of air flow in the 2nd phase of maximal expiration remained almost unchanged with hyperventilation in emphysema cases, despite an increasing rate of the peak flow. According to Sivertson and Fowler,[4] the patients with emphysema showed an increased mean rate of change in P_{ACO_2} in the 2nd phase of forced expiration after hyperventilation than that after normal breathing. However, in the present study, no significant change was observed. In emphysema it is well known that an expiratory level is elevated during hyperventilation. Furthermore, airway resistance and pulmonary pressure should be increased within the succeeding forced expiration. This appeared to reduce the pulmonary blood flow and the ratio of pulmonary blood flow per alveolar lung volume, in a manner similar to that observed with the Valsalva maneuver.[13]–[18] In this study, knowledge relating to the ratio of rate of pulmonary blood flow per alveolar lung volume throughout the entire respiratory cycle was not available, since events were limited to the expiratory phase of a single respiratory cycle.

On the analysis of an individual case, the value of initial P_{ACO_2} in the 2nd phase was slightly lower than the end-tidal P_{ACO_2}; and the average value of expired volumes in the 1st phase was substracted from the average value of tidal volumes. During natural breathing, normal subjects and patients with emphysema delivered 90 ml. and 30 ml. of pure alveolar gas respectively in each tidal air. During hyperventilation, the former delivered 1,340 ml. of pure alveolar gas and the latter 190 ml. (Table I, II). This indicates the limited ability of patients with emphysema to increase an effective alveolar ventilation voluntarily. In the same patients, the large difference between $P_{\bar{V}CO_2}$ and P_{ACO_2} observed in the 2nd phase indicates that the gas exhaled must have largely come from the alveoli with a high ventilation/pefusion ratio. The expired alveolar gas may present apparent rates of increase in P_{ACO_2} that to some extent exceed the intrapulmonary rates of increase in P_{ACO_2}. However, they afford a convenient means of contrasting the normal and emphysematous state. According to Sivertson and Fowler,[4] the normal or large apparent values of $\dot{Q}/ELV$ indicate that perfusion is not reduced but that ventilation must be increased in the overventilated alveoli. In their description, " increasing the ventilation of overventilated alveoli is relatively less effective in CO_2 elimination from the blood than is a proportionate increase in normally ventilated alveoli." These chracteristics of hyperventilated alveoli have been mentioned as ' alveolar dead space.'[19]

In patients with emphysema, it is well known that there is a marked

variation in ventilation/perfusion ratios in different parts of the lung. As DuBois[13] has described, the P_{ACO_2} have fluctuations according to 'time' or 'phase of the respiratory cycle,' in addition to distribution according to ventilation and blood flow. It has been theorized by Riley[20] that the mean arterial CO_2 tension should be identical with the mean alveolar CO_2 tension. This theoretical mean tension has been designated as 'ideal' tension by Riley.[21] Rahn[22] has shown that the P_{ACO_2} obtained by sampling from the last fraction of each tidal volume is in very close agreement with the arterial CO_2 tension in normal subjects. On the other hand, they observed on the average of a 3–4 mm.Hg higher CO_2 for the Haldane technique of sampling air than the arterial blood in normal subjects.[20][22] Even at present, a puncture method is commonly used for the analysis of arterial blood. However, this requires an arterial punture and considerable skill in the determination of arterial CO_2 tension, since any single determination of arterial CO_2 tension by the bubble method can only be read with an accuracy of ± 3 mm.Hg CO_2 tension.[23] On the other hand, methods of analyzing alveolar gas continuously offer many practical advantages, with the recent availability of the rapid infrared CO_2 analyzer (its accuracy is ± 1 mm.Hg). A rapid infrared gas analyzer has been used for the determination of $P_{\bar{v}CO_2}$ by a bag rebreathing method.[1][2][5] According to Collier,[1] if gas mixtures carefully adapted to individual requirements are used, the plateau CO_2 tension as obtained by rebreathing of a small volume of a CO_2 mixture during spontaneous breathing in about 18 seconds may represent $P_{\bar{v}CO_2}$. By this method, $P_{\bar{v}CO_2}$ can be adequately determined in patients with heart and/or lung disease, with an accuracy of ± 3 mm.Hg CO_2 tension.[1] Although it is customary to represent the degree of hypercapnia by arterial CO_2 tension, the mixed venous blood CO_2 is equally representative. The findings shown in Fig. 14 suggest that the degree of pulmonary hypertension varies directly with the severity of hypercapnia, and that hypercapnia as well as anoxia may be important in the genesis of pulmonary hypertension in patients with chronic emphysema.[7][16][24]–[26] This is supported by the general knowledge that hypercapnia is the consequence of ineffective alveolar ventilation and is always associated with anoxia unless the individual is inhaling oxygen with a partial pressure greater than that in room air. The correlation between $P_{\bar{v}CO_2}$ and pulmonary artery pressure will be useful in estimation of the pulmonary hypertension from the value of expired P_{ACO_2} instead of catheterization procedure in patients with a $P_{\bar{v}CO_2}$ of more than 55 mm.Hg.

Suskind and Rahn[27] pointed out that the A-V CO_2 difference was reasonably constant in a respiratory steady state despite a wide variation in cardiac output. In view of this finding, Collier and his coworkers[2] assumed a constant A-V CO_2 tension difference of 6 mm.Hg in both normal subjects and patients with heart or lung disease. They employed a 'rebreathing method' for determination of $P_{\bar{v}CO_2}$, and estimated the arterial CO_2 tension, substracting a fixed A-V CO_2 tension difference of 6 mm.Hg from the $P_{\bar{v}CO_2}$. In our

17 patients, the arterial blood and expired alveolar gas were sampled simultaneously. The arterial CO_2 tension was compared with the end-tidal P_{ACO_2}, the P_{ACO_2} of maximal expiration following natural breathing and the estimated $P_{\bar{V}CO_2}$ (the maximal value of forced expiration after breathholding). The end tidal-arterial CO_2 tension difference was calculated for patients with emphysema, and an average value of -10 mm.Hg was obtained (Table I).[28] In 15 of 17 patients studied, the P_{ACO_2} of maximal expiration following natural breathing equaled or exceeded the arterial CO_2 tension. On the other hand, the measured arterial CO_2 tension never exceeded significantly the estimated $P_{\bar{V}CO_2}$ in all cases. Though Defares[5] recently calculated the cardiac output using the indirect Fick's principle in normal subjects, with the aid of the rebreathing method for the estimation of $P_{\bar{V}CO_2}$ and sampling the end-tidal air for the substitution of arterial CO_2 tension, the precision of the rebreathing method, as well as breathholding method, appeared to be too unsatisfactory for the determination of cardiac output. As mentioned above, the A-V CO_2 tension difference at rest is about 6 mm.Hg, and an accuracy of about 0.5 mm.Hg would be necessary for the determination of cardiac output. Moreover, the end-tidal P_{ACO_2} may be considerably lower than the arterial CO_2 tension in patients with pulmonary emphysema, which would make the determination of cardiac output by this method impractical or less accurate.

Summary and Conclusion

Continuous analysis of expired alveolar CO_2 tension, using a rapid infrared meter, was made in 10 normal subjects, and 20 patients with chronic pulmonary diseases. An analytical method similar to that previously described by Sivertson and Fowler was used. Arterial blood was sampled and arterial CO_2 tension was measured in 17 patients simultaneously with expired alveolar CO_2. Right heart catheterization was carried out in 38 patients with pulmonary emphysema.

(1) In many patients, the resting end-tidal CO_2 tension was frequently less than normal. In both normal subjects and patients, the upward slope of alveolar CO_2 tension decreased toward the end of forced expiration. However, in patients with emphysema a larger rate of increase in expired alveolar CO_2 tension, smaller expired volumes and the prolonged duration of forced expiration were observed. In patients, the apparent values of the difference between mixed venous and alveolar CO_2 tension were large and the percentage rates of decrease in the difference were normal. This probably indicates that perfusion is not reduced in the overventilated alveoli of the emphysematous lung. These results well coincided with Fowler's observations.

(2) In cases of pulmonary emphysema, the mean rates of increase in expired alveolar CO_2 tension observed during a forced expiration after hyperventilation, remained similar to those observed during a forced expiration after normal breathing. An expiratory level was elevated in patients with emphysema during

hyperventilation. Within the succeeding forced expiration, air-way resistance and pulmonary pressure must have been increased, consequently the ratio of pulmonary blood flow per alveolar lung volume should be reduced.

(3) In many patients, the end-tidal CO_2 tension was lower than the arterial CO_2 tension, but the maximal CO_2 tension of the forced expiration following normal breathing equaled or slightly exceeded the arterial CO_2 tension. On the other hand, the measured arterial CO_2 tension never exceeded the estimated mixed venous CO_2 tension significantly.

(4) In pulmonary emphysema, the elevated values of mixed venous CO_2 tension well correlated with the degree of pulmonary hypertension. This correlation is proposed for the use in estimating the pulmonary hypertension from the value of expired alveolar CO_2 tension in patients with a mixed venous CO_2 tension of more than 55 mm.Hg.

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Effects of Insulin on the Electrocardiogram

Saburo MASHIMA, M.D.

Marked flattening of the T-wave was observed frequently after intravenous administration of insulin and was closely related to the serum K level. Infusion of KCl solution abolished the T-wave change partially or completely. Adrenalin released by hypoglycemic reactions seemed to enhance the insulin induced hypopotassemia. All of the electrocardiographic changes, however, could not be explained by the hypopotassemic theory alone. Possible mechanisms are discussed. Changes in the T-vector after insulin injection were also investigated.

ELECTROCARDIOGRAPHIC changes produced by the administration of insulin have frequently appeared in the literature,[1)–10)] and the underlying mechanisms of these changes and their clinical significance have been discussed by many investigators. The changes reported in the previous studies include flattening or inversion of the T-wave, depression of the ST-segment, prolongation of the QT-interval, changes in the P-wave and the QRS-complex, prominence of the U-wave and various arrhythmias.

Some earlier investigators ascribed them to the changes in myocardial nutrition, to the altered tone of autonomic nervous system or to the direct action of insulin on the myocardium.[1)–7)] But with increasing evidences for release of sympatheticomimetic amines from adrenals in hypoglycemia,[11)–13)] and with clearer recognition of electrocardiographic changes in hypopotassemia,[14)15)] the role of these amines and serum potassium concentration, which is well known to be lowered by insulin,[16)17)] have been drawing particular attention as the cause of the electrocardiographic changes.[5)–9)]

The present study is mainly concerned with the serial electrocardiographic observations after intravenous insulin with or without infusion of KCl solution or injection of hexamethonium was given to diabetic and non-diabetic patients and with similar observations after subcutaneous administration of adrenalin. The mechanisms of the electrocardiographic changes, especially those of the T-wave changes were discussed.

Materials and Methods

Sixty-two experiments of four different types were performed in 42 cases which consist of 24 diabetic and 18 non-diabetic patients (Table I). In the diabetic group, there were 6 cases with hypertensive and/or sclerotic heart disease. In the non-diabetic group, 5 cases with hypertensive and/or sclerotic heart disease and 2 cases

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Table I. Numbers of Cases

	Non-diabetic	Diabetic	Total
Insulin	16 (5)*	24 (6)	40 (11)
Insulin with KCl	2 (0)	3 (0)	5 (0)
Adrenalin	5 (0)	5 (0)	10 (0)
Insulin with Hexamethonium	4 (0)	3 (0)	7 (0)

* Cases with heart disease.

with liver cirrhosis were included and the remaining cases had no cardiovascular or metabolic disease.

Insulin Test—0.1u/Kg. of regular insulin was given intravenously to 24 diabetic and 16 non-diabetic patients in the fasted state. Electrocardiograms were taken with a conventional amplifier type instrument with photographic recording and three standard leads and six precordial leads were used. In order to maintain precordial leads at a constant position, small electrodes were fixed to the chest wall throughout the experiment. The tracings were recorded immediately before and at 15, 30, 45, 60 and 120 minutes after injection. To determine the change in the T-wave height accurately, a ratio between the height of the T-wave and that of the R-wave was measured with arbitrary selected lead V_5. Simultaneously with electrocardiographic recordings, blood samples were taken from the antecubital vein for the determination of blood sugar and serum potassium concentration. Blood pressure was frequently measured up to 60 minutes and also measured at 120 minutes after injection.

KCl-Insulin Test—Within a week after the first experiment with insulin, the same procedure was repeated in 5 patients with continuous intravenous infusion of 20 to 50 mEq./L. KCl in normal saline. The infusion was continued approximately for 60 minutes at a rate of 5 to 10 ml./min. This test was undertaken to see whether the infusion of KCl could prevent the electrocardiographic changes produced by the insulin.

Adrenalin Test—To clarify the mechanism of the electrocardiographic changes produced by insulin, 13 micrograms/Kg. of adrenalin was injected subcutaneously to 5 diabetic and 5 non-diabetic patients, then the observations were made in the same manner as in the insulin test and the results of two experiments were compared. In the total of 10 cases studied, 8 had also insulin test a few days prior to the present experiment.

Hexamethonium-Insulin Test—To suppress the release of sympatheticomimetic amines from adrenals and other tissues, intravenous dosage of 1mg./Kg. hexamethonium bromide was given immediately before insulin injection to 3 diabetic and 4 non-diabetic patients with normal blood pressure. This test was performed within a week after the first experiment with insulin alone and serum potassium levels were compared. Electrocardiogram was not taken during this experiment since hexamethonium alone could produce some electrocardiographic changes.

Blood sugar determinations were made by Hagedorn-Jensen's method. Serum potassium concentrations were determined by flame photometry.

Results

Insulin Test—

The patients are divided into two groups in accordance with the presence or absence of the hypoglycemic reactions. It was considered to be a positive reaction when incrase in systolic blood pressure or decrease in diastolic blood pressure was more than 20 mm.Hg and pulse pressure increased more than 20 mm.Hg or the patient showed marked sweating. Four diabetic and 9 non-diabetic patients had the positive reaction. These reactions occurred less frequently in the diabetic group and when they occurred, they were usually later in time than in the non-diabetic group. All 9 non-diabetic cases developed these reactions about 30 minutes after the injection with exception of 2 cases with liver cirrhosis, in which the reactions occurred 40 to 50 minutes after the injection. While in the diabetic group, all 4 cases developed the reactions 45 minutes after insulin injection or later.

The electrocardiographic changes observed are summarized in Table II.

Table II. Electrocardiographic Changes after Intravenous Injection of Insulin

Hypoglycemic Reaction	Non-diabetic (+)	Non-diabetic (−)	Diabetic (+)	Diabetic (−)	Total
Numbers of Cases	9	7	4	20	40
Numbers of Cases with Heart Disease	1	4	1	5	11
Tachycardia (20% or more shortening of the RR-interval)	6	1	3	1	11
Arrhythmias and Bundle Branch Block	2	1	1	1	5*
Changes in the P-wave	6	1	2	4	13**
Prolongation of the PQ-interval (0.02 sec. or more)	0	1	0	2	3
Shortening of the PQ-interval (0.02 sec. or more)	2	0	0	0	2
Depression of the ST-segment (0.05mV or more in any lead)	3	3	1	1	8
Flattening of the T-wave (20% or more decrease in the T/R ratio in V_5)	8	6	2	18	34
Prominence of the U-wave	3	3	2	1	9
Decrease in Serum K (10% or more)	9	5	4	15	33

* Multiple ventricular extrasystoles in 2 cases, occasional ventricular extrasystoles in 2 cases and transient right bundle branch block in one case.

** Increase in the height of P_{II} or P_{III} in 6 cases, decrease in it in 3 cases and changes in breadth or shape in any lead in 4 cases.

Among the various electrocardiographic changes, the T-wave changes occurred most frequently, and in 34 out of 40 cases studied there occurred more than 20% decrease in T/R ratio in V_5 from the control value (Table II). In other leads, the upright T-wave usually decreased in its height, and in some cases the inversion of the T-wave occurred. There were 3 cases with previously inverted T-wave in the left precordial leads and it deepened in 2 cases and showed little change in one case. Detailed discussion concerning these changes in various leads will be given later.

A case with marked decrease in the height of the T-wave is shown in Fig. 1. The values of blood sugar, serum potassium concentration and the

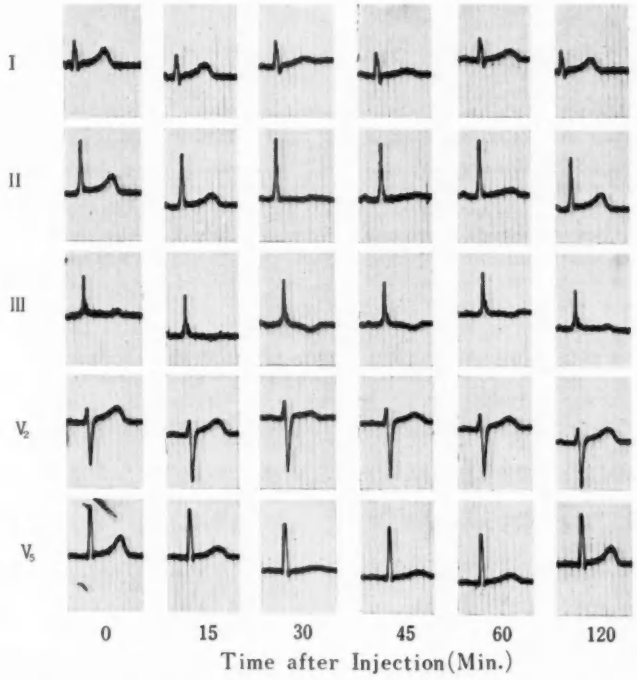


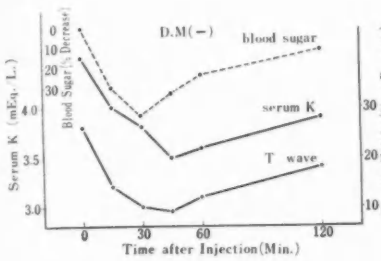
Fig. 1. Electrocardiograms after insulin injection in a 19-year-old normal male with positive hypoglycemic reactions.

height of the T-wave are given in Table III, and time course of their average values are in Fig. 2 and 3. It can be seen that the decrease in T-wave height and serum potassium concentration are approximately parallel. Features of the T-wave change were essentially not different in the diabetic and non-diabetic group but its occurrence was later in the diabetic group than in the non-diabetic group.

In Fig. 4, decrease in the T-wave height at 15 and 30 minutes after injection

Table III. Blood Sugar, Serum Potassium Concentration and T-wave Height after Intravenous Injection of Insulin

	Cases	Sex and Age	Blood sugar (mg./100 ml.) Time in min. after injection 0	15	30	45	60	120	Serum K (mEq./L.) Time in min. after injection 0	15	30	45	60	120	T-wave height (% to R-wave) Time in min. after injection 0	15	30	45	60	120	Hypoglycemic reaction
Non-diabetic	1. S. M.	63M	93	62	49		62	74	4.2	3.9	3.5		3.6	3.7	46	43	27		25	41	(−)
	2. T. S.	25M	92	35	41	71	69	71	4.2	3.6	3.2	2.8	3.3	3.9	28	22	14	11	13	24	(−)
	3. M. S.	43M	105	75	68	63	76	79	4.6	4.1	4.2	4.2	4.2	4.2	12	8	6	2	8	9	(−)
	4. M.H.	43M	105	75	67	82	90	107	5.4		5.0	4.8	4.9	5.1	14	7	6	6	7	11	(−)
	5. T. I.	61F	101	78	78	76	78	99	3.7	3.2	3.4	3.3	3.2	3.2	0	0	0	0	0	0	(−)
	6. T. O.	41M	90		58	64	75	81	4.4	4.1	4.4	4.6		4.7	30		22	27	25	27	(−)
	7. M. T.	46F	96	71	47	58	64	87	5.1	4.7	4.5	4.4	4.4	4.4	10	0	−5	−10	−15	−10	(−)
	8. Y. I.	19M	91	76	57	76	78	90	4.7	4.1	3.7	3.5	3.8	3.9	48	28	23	24	29	32	(+)
	9. T. T.	20F	93		59	44	59	73	4.0	3.4	3.1	2.8	3.0	3.1	24	14	10	13	13	13	(+)
	10. K. N.	62M	89		45	60	57		5.4		3.9	3.2	3.2								(+)
	11. K. Y.	21M	98	60	48	54	68	80	4.8	4.4	4.2	3.4	3.6	4.1	34	18	3	7	15	32	(+)
	12. Z. K.	34M	114	78	74	83	85	124	4.6	4.2	3.5	3.0	2.9	3.2	35	22	17	16	18	27	(+)
	13. M. T.	65F	133	106	73	67	67	118	4.2		3.5	3.4	3.0	2.9	21		9	5	5	5	(+)
	14. Y. Y.	26F	91	48	43	60	74	72	4.4	4.2	3.8	3.8	3.7	3.9	24	16	16	18	22	23	(+)
	15. K. K.	47M	94	58	58	64	69	88	4.5	3.9	3.7	3.3	3.5	3.4	38	18	9	9	12	23	(+)
	16. A. K.	13F	90	60	56	71	82	87	4.4	3.8	3.6	3.4	3.8	3.2	25	20	8	0	5	20	(+)
	Average of 15 cases (10. K.N. excluded)								4.5	4.0	3.8	3.5	3.6	3.9	26	14	10	9	12	18	
Diabetic	1 K. H.	56M	100	85	74	69	76	85	3.4	3.2	3.1	3.2	3.0	3.2	29	16	14	17	20	29	(−)
	2 H. O.	43M	231		188	166	162	160	4.3	3.8		4.0	3.9	3.8	36	28	27	27	30	22	(−)
	3 T. K.	45F	385		374	322	344	364	4.9		4.6		4.4	4.3	57	50	49	50	50	54	(−)
	4 S. O.	53M	163		127	118	111	116	3.9		3.7		3.7	3.9	60	38	38	43	47	40	(−)
	5 A. H.	25F	173		111	93	73	81	3.9		3.5	3.6	3.5	3.6	0	0	0	0	0	0	(−)
	6 K. H.	64F	170		85	62	60	74	4.7		3.9	4.0	3.4	3.4	21	6	6		5	4	(−)
	7 S. S.	47F	121		60	52	61	118	4.8		4.1	3.5	3.1	3.8	17	8	8	14	8	13	(−)
	8 A. K.	58F	161		84	68	68	99	5.0		3.6	3.8	3.7	3.3	8	2	2	2	2	2	(−)
	9 K. Y.	69M	182		116	115	96	82	4.5		4.4	4.2	4.0	3.7	40	27				26	(−)
	10 S. M.	68M	281		170	137	117	125	4.8		4.8	4.7	4.8	4.9	10	8	10	12	12	12	(−)
	11 Y. S.	57M	198		160	148	140	127	4.4		4.0	4.0	4.1	4.0							(−)
	12 T. U.	53F	223		178	163	160	130	4.7		4.0	4.2	4.3	4.2	33	23	26	25	31	31	(−)
	13 Y. I.	40M	240	208	170	160	156	146	3.7	3.4	3.3	3.5	3.8	3.9	32	16	18	23	27	25	(−)
	14 I. Y.	40M	113	110	107	96	96	89	4.0	3.6	3.8	3.4	3.8	3.6	19	14	14	15	15	16	(−)
	15 G. O.	63M	174	134	95	77	68	94	3.9	3.4	3.5	3.6	3.6	3.5	10	6	4	6	4	1	(−)
	16 T. K.	31M	242	190	131	112	113	108	4.1		3.7		3.8	4.1	50	40	35	44	39	39	(−)
	17 T. O.	45M	162	142	123	115	120	128	3.6	3.2	3.3	3.5	3.6	3.8	3	3	− 1	− 6	− 2	4	(−)
	18 S. Y.	57F	295		232	211	207	161	3.5		3.4		3.4	3.3	−24	−24	−26	−26	−27	−27	(−)
	19 S. S.	60M	142		90	75	74	89	3.7		3.0		3.1		− 8	−20	−23	−20	−18	−18	(−)
	20 T. A.	55M	174	156	145	146	141	137	4.5	4.3	4.4	4.5	4.5	4.5	− 2	− 2	− 2		− 2	− 1	(−)
	21 Y. W.	56M	130	89	59	43	59	93	3.6	3.2	3.3	3.2	2.9	3.0	53	29	36	13	13	17	(+)
	22 S. F.	58F	152		57	47	66	97	4.1		3.8	3.8	3.6	3.7	23	9	10	2	4	12	(+)
	23 K. O.	53F	128	68	52	41	51	60	4.1		3.5	3.2	2.9	3.7	33	24	14	6	10	16	(+)
	24 K. T.	55M	115		84	73	66	79	3.4	3.1	3.1	3.3	3.2	2.8	12	6	6	6	8	6	(+)



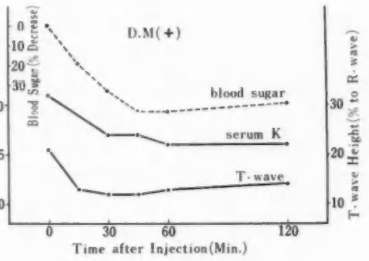


Fig. 2 (Left). Time courses of blood sugar, serum K and T-wave height after insulin injection (average of 15 cases of the non-diabetic group).

Fig. 3 (Right). Time courses of blood sugar, serum K and T-wave height after insulin injection (average of 23 cases of the diabetic group).

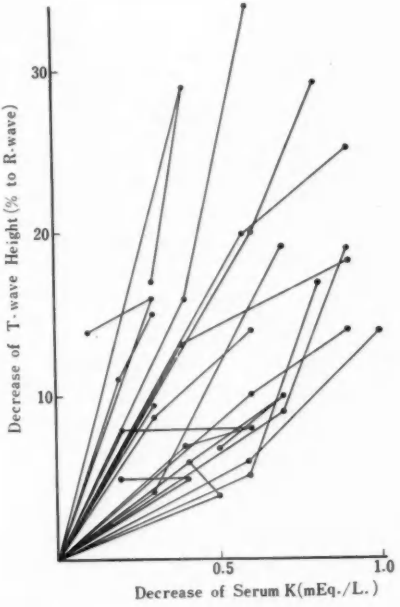


Fig. 4. Decrease in the T-wave height plotted against that of serum K. (Values at 0, 15 and 30 minutes after insulin injection are shown.)

of insulin was plotted against that of serum potassium concentration. The direction of each line differs from case to case, which is, in part, due to the difference in the initial height of the T-wave. But in most cases, the points representing before and 15 and 30 minutes after injection are connected by an approximately straight line, which means the quantitative relationship of

the T-wave height and the serum potassium concentration at least up to 30 minutes after injection.

These relationships, however, are not maintained throughout the experiment especially more than 30 minutes after the injection. This will be mentioned later.

KCl-Insulin Test—

In view of the gross parallelism between the serum potassium level and the T-wave height, potassium chloride was given with insulin to prevent the T-wave changes in 5 cases. In 2 out of 5 cases, both serum potassium concentration and the T-wave height were kept above the preinjection level during the infusion of potassium chloride. The other 3 cases showed a decrease in both the T-wave height and serum potassium concentration, but the changes were not marked as those with insulin alone. Time courses of their average value in 4 cases are shown in Fig. 5. In the remaining case, the infusion was too slow to produce any difference from the control experiment.

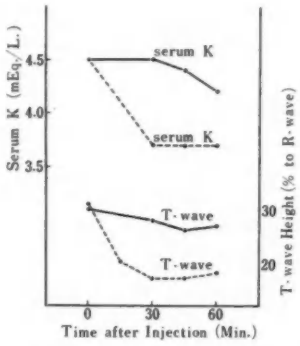


Fig. 5. Time courses of serum K and T-wave height after insulin injection with (———), and without (- - - - -) KCl (average of 4 cases).

Adrenalin Test—

Effects of adrenalin on the electrocardiogram and on the serum potassium level were compared with those of insulin, for the release of adrenalin is said to occur in the hypoglycemic state. In this experiment, the average value of maximal rise of blood pressure in 10 cases was 36 mm.Hg and that of blood sugar was 50 mg./100 ml. The T-wave change was similar to that of insulin test and seen in all cases. Electrocardiographic changes are summarized in Table IV and time courses of the T-wave height and the serum potassium concentration are parallel (Fig. 6).

Hexamethonium-Insulin Test—

Hexamethonium was used to prevent the release of sympatheticomimetic amines with hypoglycemic reactions. Results are shown in Fig. 7. A case

Table IV. Electrocardiographic Changes after Subcutaneous Injection of Adrenalin

Number of Cases	10 (5*)
Tachycardia (20% or more shortening of the RR-interval)	10 (5)
Arrhythmias	2 (2)
Changes of the P-wave	7 (3)
Shortening of the PQ-interval (0.02 sec. or more)	2 (0)
Depression of the ST-segment (0.05 mV or more in any lead)	3 (2)
Flattening of the T-wave (20% or more decrease in the T/R ratio in V_5)	10 (5)
Prominence of the U-wave	6 (1)
Decrease in Serum K (10% or more)	10 (5)

* Cases with heart disease.

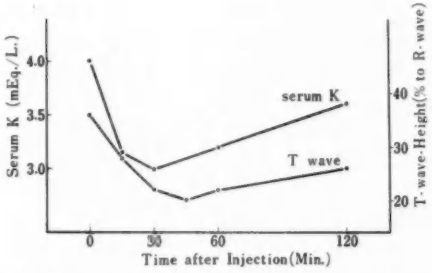


Fig. 6. Time courses of serum K and T-wave height after subcutaneous injection of adrenalin (average of 9 cases).

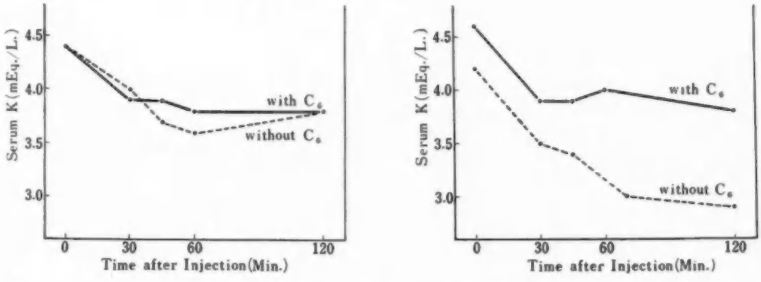


Fig. 7. Serum K after insulin injection with (———) and without (- - - - -) hexamethonium.

Left : Average of 7 cases.

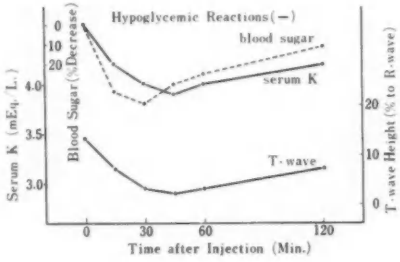
Right: An example of 65-year-old female. Hexamethonium showed marked effect in this case.

with marked effect of hexamethonium is also shown in Fig. 7.

It can be seen that the hypopotassemia occurring up to 30 minutes after insulin injection was not prevented by hexamethonium but in the later period of the experiment, decrease in the serum potassium concentration was relatively less than that with insulin alone. The effect of intravenous hexamethonium is said to continue about 60 minutes and the results have to be compared within this range. In general, blood pressure falls and pulse rate increases after hexamethonium injection but all of the 7 cases had no complaint throughout the experiment.

Insulin Test and the Hypoglycemic Reactions—

The curve of serum potassium concentration in Fig. 2 seems not to be a smooth line, and when the blood sugar, serum potassium and the T-wave height were averaged with the hypoglycemic and non-hypoglycemic group separetely, the results are in Fig. 8 and 9 and the curve of the serum potas-



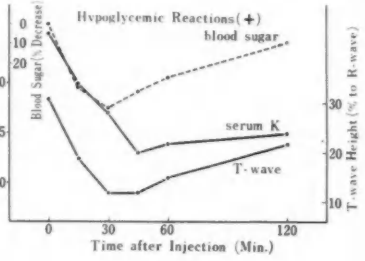


Fig. 8 (Left). Time courses of blood sugar, serum K and T-wave height (average of 5 cases of the non-diabetic non-hypoglycemic group).

Fig. 9 (Right). Time courses of blood sugar, serum K and T-wave height (average of 8 cases of the non-diabetic hypoglycemic group).

sium seems smoother in the non-hypoglycemic group than in the hypoglycemic group. This is well demonstrated in Fig. 10 where a case in the diabetic group is shown.

Further comparison of both groups reveals that the hypoglycemic group showed maximum decrease of 1.3 mEq./L. in the serum potassium concentration, and at 120 minutes after insulin injection it still remained 1.2 mEq./L. below the preinjection level (average of 9 cases of which one was omitted from Fig. 8 owing to the lack of the T-wave data), while the corresponding value of the non-hypoglycemic group was 0.4 mEq./L. Although these results may in part be due to the fact that insulin sensitivity is higher in the hypoglycemic group than in the non-hypoglycemic group, the shape of curves and the prolonged decrease in the serum potassium concentration in the hypoglycemic group is strongly suggestive of the contribution of the hypopotassemic action of sympatheticomimetic amines, which is responsible to the second flattening of the T-wave.

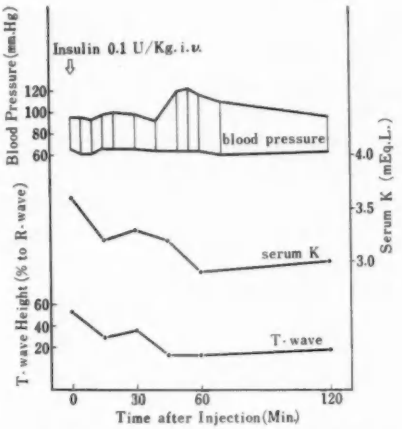


Fig. 10. A case with marked hypoglycemic reactions and biphasic curves of serum K and the T-wave height (a 56-year-old male).

These results may indicate that adrenalin or the related amines affect the T-wave probably by way of serum patassium concentration. The relationship of the T-wave and the serum potassium level is, however, not necessarily quantitative throughout the experiment. For instance, the time relation of maximum changes in the serum potassium level and the T-wave height is seen in Table V, where 29 cases with more than 20% decrease in the T-wave

Table V. Time Relation of Maximal Decreases in the T-wave Height and the Serum K Concentration after Intravenous Injection of Insulin

		T Precedes (cases)	K Precedes (cases)
Hypoglycemic Reaction	(+)	10	1
	(—)	6	7

Note: Cases in which the peak of both changes occurred at the same time were omitted.

height and 10% or more decrease in the serum potassium concentration are examined. It is clear that in the hypoglycemic group, the peak of the T-wave change precedes that of the serum potassium concentration in most cases, which can hardly be explained by the assumption that all of the T-wave changes are evoked by the hypopotassemia alone.

Discussion

That the changes in the T-wave occurred most markedly and frequently after insulin injection when they are compared with other electrocardiographic changes is in fair agreement with previous reports. Wittgenstein,[1] who was

one of the earliest investigators of the T-wave changes produced by insulin, considered them to be due to the lowered blood sugar level itself. However, it was disagreed by Haynal,[2] who observed that the injection of glucose failed to restore the T-wave changes caused by the insulin. This was also confirmed in the present study and the direct relationship between the T-wave and the blood sugar level was excluded.

On the other hand, hypopotassemia has been said to lower the T-wave[14][15] and it is also evident in this study that there is gross parallelism between the height of the T-wave and the serum potassium level. The quantitative relation between them was well established at least up to 30 minutes after insulin injection. These results together with the fact that the infusion of KCl prevented the T-wave changes caused by insulin to a certain extent indicated that not only a close relation but a causative relation could exist between them.

As already mentioned, the release of adrenalin or the related amines has been considered an important factor to the electrocardiographic changes.[6][7] In the present study, adrenalin administration produced similar changes to those produced by insulin in several points, and so far as the height of the T-wave was concerned, the two drugs produced almost undistinguishable changes. Moreover, the T-wave changes produced by adrenalin again was parallel to the decrease in the serum potassium concentration. Prolonged decrease in serum potassium level in the hypoglycemic group and the preventive action of hexamethonium on the lowering of the serum potassium level more than 30 minutes after insulin injection also indicate that the release of adrenalin occurs during the hypoglycemic reactions and contribute to the lowering of the serum potassium level. In two cases of liver cirrhosis, the size of spleen markedly decreased at the time of the hypoglycemic reactions, which might offer an additional evidence for the increased adrenalin secretion during hypoglycemia.

Although adrenalin is believed to lower the serum potassium level, which, in turn, affects the T-wave, the relation between the serum potassium and the T-wave is quantitative only within 30 minutes after insulin administration. Especially, the fact that the peak of the T-wave change precedes that of the serum potassium in most cases of the hypoglycemic group can hardly be compatible with the concept that all the T-wave changes are due to the lowered serum potassium level alone and it must be postulated that there might be some earlier acting mechanisms. In the non-hypoglycemic group there were some cases in which the maximal change in the T-wave preceded that in the serum potassium, but in this group, a mild degree of hypoglycemic reaction might have existed; in fact, various degrees of tachycardia were observed in most cases.

Possibly, the increased sympathetic tone and resulting changes in hemodynamics may play a part in the mechanisms of the T-wave change in the hypoglycemic state. Results of the adrenalin test indicated that subcuta-

neoulsy injected adrenalin usually did not lower the T-wave earlier than the changes in serum potassium, while in 5 cases the rise of blood pressure occurred earlier than the T-wave change. It seems, therefore, that the blood pressure is not necessarily of primary importance to the T-wave change, but the time relation between these changes was not always a constant one that a general conclusion could not be drawn. Mitchell and Shapiro[18] repored the lowering of the T-wave in the anxiety state. Cannon and Sjöstrand[19] observed the electrocardiograms similar to those seen in hypopotassemia immediately after intravenous administration of adrenalin. If the action of endogenous hormone is similar to that of intravenous adrenalin in their experiment, this may also contribute to the T-wave changes in the hypoglycemic reactions.

Weil-Marherbe[20] demonstrated that the blood level of catecholamines decreased after insulin injection and suggested the increased tissue consumption of these amines. This may lead one to the concept that all the serum potassium changes after insulin injection could be evoked by means of catecholamines. But it seems unlikely that the action of the two drugs on serum potassium occurs in the same manner in every aspect, since their effect on the carbohydrate metabolism is different and there is also a certain point of difference in the effect on the potassium metabolism.[21][22] The present study does not offer any information concerning this problem. Hexamethonium has no effect on the circulating catecholamines which already exist in the blood before its administration.

As for the hypopotassemic action of insulin, it has been said that a shift of potassium to the liver occurs with increased glycogen deposition or simply that potassium is related to the carbohydrate metabolism in the liver.[21][23] Adrenalin has been known to induce transient hyperpotassemia when injected intravenously, which is immediately followed by hypopotassemia[24][25] and this is said to be due to the potassium shift from the blood to the peripheral tissues or also to the liver.[22][25]

A possible explanation of adrenalin-induced hypopotassemia is to postulate that extracellular K^+ ion exchanges with intracellular H^+ ion which is derived from the intermediate metabolites of the carbohydrate. As is well known, adrenalin increases the lactate content of the blood, that is, the metabolites themselves may appear in the blood, but H^+ ion will probably move across the barrier of the cell membrane more freely than other ions. Although various buffer mechanisms would not allow an appreciable change in pH of the blood or cells, slight decrease in the pH of the effluent from the perfused frog liver after adrenalin was reported recently.[26] The hepatic potassium output observed initially may be related to the glycogenolytic action of adrenalin. Lactic acidemia after the administration of insulin is less marked but the mechanisms mentioned above may also contribute to the hypopotassemia induced by the insulin. Extracellular alkalosis may lead to similar exchange process and the recent reports[27][28] of inverse relationship between the serum K and the blood pH can be explained on the basis of this process.[29]

On the other hand, Magida and Roberts[30] reported that electrocardiographic changes similar to those seen in hypopotassemia occurred in the extracellular alkalosis and considered that alterations of the hydrogen ion gradient across the cell membrane might be responsible to these changes. If this is the case, it is suggested that under the action of intravenous adrenalin or in the hypoglycemic state, the same intracellular or exchange process is acting on the T-wave on the one hand and on the potassium metabolism on the other.

Changes in the T-vector: Hypopotassemia observed in the present study was relatively mild and the value below 2.0 mEq./L. was never encountered, and the normal T-vector usually seemed not to change its direction corresponding to the flattening of the T-wave in all leads. However, the inversion of the T-wave occurred in some cases (Fig. 1). Also, severe hypopotassemia has been reported to induce the inversion of the T-wave in an extensive degree. As for the abnormal T-wave, it has been said that the changes in the T-wave of ventricular hypertrophy and of myocardial infarction are opposed in direction after administration of potassium salts,[15][31] and the T-vector changes after administration of KCl under various conditions were also reported.[32]

Under these circumstances, additional experiments with insulin were performed with X, Y and Z leads of SVEC III system[33] to construct the mean T-vector in 4 cases with normal electrocardiogram and in 3 hypertensive cases with inverted T-wave in the left precordial leads. In normal cases, the T-vector seemed to decrease in magnitude without appreciable change in its direction after insulin injection. An example is seen in Fig. 11. Results of 2 out of 3 hypertensive cases are illustrated in Fig. 12 and 13 (In the remaining case, changes in the T-vector were small). In the horizontal plane, clockwise rotation of the T-vector occurred in both cases and in one case it occurred also in the frontal plane. There was no remarkable change in the QRS-vector, but when the ventricular gradient vector G was constructed from the QRS- and T-vectors, the direction of changes in the T-vector was approximately paralleled to the direction of the G-vector, from which the constancy of the G-vector direction throughout the experiment resulted. From this point of view, the directional change in the normal T-vector is small because the direction of the G-vector is approximated by that of the T-vector. The inversion of T_{III} in the case illustrated in Fig. 1 can be explained on the same basis, for in this case, the T-vector is situated to the left of the QRS-vector.

The results obtained here, although the paucity of cases did not allow to draw a general conclusion, suggest that the direction of the T-vector changes in such a way that the ventricular gradient does not change its direction.

Electrocardiographic Changes Other than Those in the T-Wave—(Table II)

Increase in size of the P-wave was observed more frequently than previously reported, especially in connection with tachycardia. But these were of mild degree so that the previously normal P-wave remained all within the

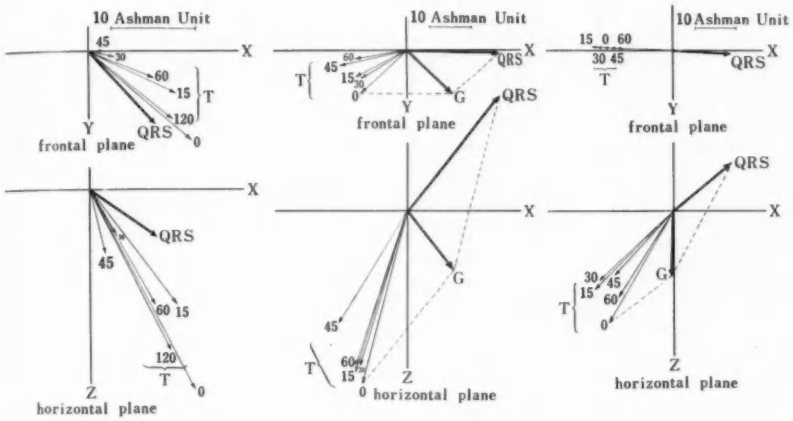


Fig. 11 (Left). Changes in the T-vector after insulin injection in a normal case. Numbers indicate the time in minutes after injection.

Fig. 12 (Middle). and Fig. 13 (Right). Changes in the T-vector after insulin injection in two hypertensive cases with inverted T-wave in the left precordial leads. Numbers indicate the time in minutes after injection.

normal limits.

Depression of the ST-segment occurred in 4 out of 11 cases with heart disease and was also seen in 4 out of 13 hypoglycemic cases. This may be related to myocardial damage.

Two cases of multiple ventricular extrasystole and a case of transient right bundle branch block had heart disease and developed similar arrhythmias or block during the exercise test performed before the insulin experiment. One case out of them developed extrasystoles of multifocal type and severe hypoglycemic reactions at the same time. This arrhythmia continued more than 30 minutes and disappeared within 5 minutes after intravenous administration of 10 gm. glucose. Serum potassium level became lower after the administration of glucose. In another case, multiple extrasystoles of the fixed coupling type were seen in the tracing of 30 minutes after insulin administration and disappeared at 60 minutes. Again, serum potassium was lower at 60 minutes than at 30 minutes after the injection of insluin. In these cases, therefore, hypopotassemia seemed not to be the main cause of the arrhythmias, although low potassium medium has been known to increase the excitability of myocardium.[34]

The clinical implication of above results is that the flattening of the T-wave is reversible and is not necessarily related to the myocardial damage, but special caution should be taken to the hypoglycemic reactions, especially in patients with heart disease, who might be very sensitive to these reactions.

Summary

(1) After intravenous administration of insulin, serial observations of electrocardiograms with blood pressure, blood sugar, and serum potassium concentration were made and in order to clarify the underlying mechanisms of the resulting electrocardiographic changes, similar observations after administration of insulin together with infusion of KCl solution or with hexamethonium injection and after subcutaneous administration of adrenalin were also made.

(2) Among the various electrocardiographic changes observed after insulin injection, flattening of the T-wave was the most marked and frequent, and was closely related to the serum K level especially in the earlier part of each experiment. Moreover, the T-wave changes were abolished partially or completely by KCl infusion.

(3) In the cases with hypoglycemic reactions in the insulin experiment, time courses of the T-wave height and serum K concentration seemed to follow uneven curves and hypopotassemia was severe and prolonged. From these results and the results of the adrenalin experiment and hexamethonium-insulin experiment, it was concluded that adrenalin released with hypoglycemic reactions contributed to the insulin-induced hypopotassemia in the later part of the insulin experiment.

(4) In most cases with hypoglycemic reactions in the insulin experiment, maximal change in the T-wave preceded that in serum K, which indicated that the T-wave changes produced by insulin could not be explained by the hypopotassemia alone.

(5) Nature of the T-vector changes after administration of insulin and mechanisms of the hypopotassemic action of adrenalin and insulin were discussed.

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Respiratory Findings in the Neurocirculatory Asthenia

Eiichi KIMURA, M.D.*

The most patients with neurocirculatory asthenia have some respiratory complaints. Analysing the respiratory curves recorded by metabulator, the following findings were observed as objective characteristics: irregularity of the depth of respiration, sigh, fluctuation of the respiratory level, disorder of the respiratory curve due to environmental stimulation, and augmentation of the ventilation equivalent. Especially, the value of the standard deviation divided by the mean value of the amplitudes of the breaths can serve as an index for the diagnosis of this disease.

IT has been known that most cases of neurocirculatory asthenia (NCA) have complaints concerning breathing. As Cohen *et al.*[1] described, the patients with this condition commonly express their distress as "breathlessness," "unsatisfactory breaths," "sighing," "smothering," and so on.

Unfortunately, this disease has no specific objective findings and perplexes us in making diagnosis. Although the NCA patients complain chiefly of cardio-respiratory discomfort, we often cannot find any reliable findings concerning the circulatory functions. The lowering or inversion of the T-wave in upright position is considered to be a characteristic sign by some authors,[2)-4)] however, in my own experience, this finding is observed often in hypotonic patients without neurocirculatory asthenia and sometimes even in healthy individual. Therefore, it seems that this ECG sign cannot be regarded as specific for this disease. The purpose of this paper is to find some reliable findings in NCA.

Materials and Methods

Twenty-five cases of the in- and out-patients of neurocirculatory asthenia were examined. These patients complained of cardiac discomfort without any demonstrable organic cardio-circulatory or respiratory diseases proved by physical examination. Of 25 cases studied, 15 were male and 10 female, ranging in age from 18 to 50 years. For the control, 16 healthy persons were also examined, of which 10 were male and 5 female, ranging in age from 25 to 45 years. They had no history or sign of organic cardio-circulatory or respiratory diseases.

Cardio-pulmonary function tests were carried out and the respiratory curves were recorded by Sanborn metabulator.

Results

Irregularity of the Depth in the Respiratory Curves—

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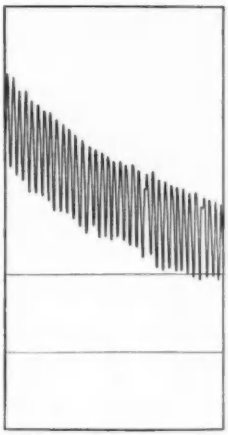
The depth of respiration is usually uniform in healthy individual, as shown in Fig. 1, while, in NCA, it was varied breath by breath, as indicated in Fig. 2. This abnormality was seen not only in the inspiration phase but in the expiration as well.



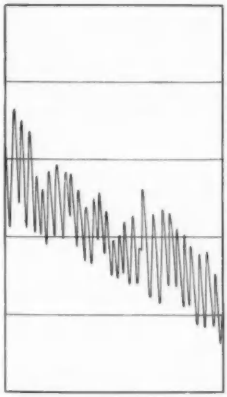


Fig. 1 (Left). The respiratory curve of a healthy person. No irregularity is observed.

Fig. 2 (Right). The respiratory curve of a patient with neurocirculatory asthenia, 41 of age, female. The depth of respiration is quite irregular.

In order to compare the irregularity of the depth of the breaths numerically, the mean value (M) and its standard deviation (σ) of the amplitude of approximately thirty breathings in the respiratory curves were calculated. The value of the latter divided by the former (σ/M) may be used as an index for the degree of irregularity. The larger value indicates the marked irregularity in the depth of respiration, while the smaller value the slight. Using this index has also been suggested by Cohen and White.[5]

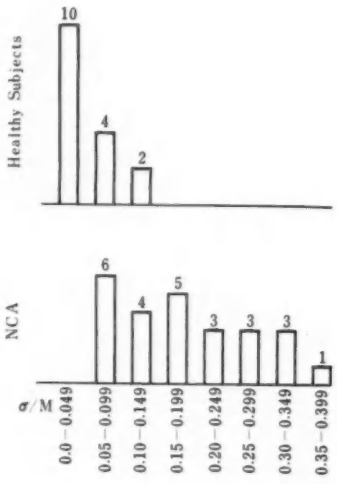
As seen in Fig. 3, all of the healthy individual showed a value below 0.15. On the other hand, the value in NCA distributed in the range from 0.05 to 0.35, and only two-fifth showed a value below 0.15. More than one half of the healthy showed a value of 0.0 to 0.049, while none of NCA showed this range of value. It is needless to say, that the difference is statistically significant.

Such an irregularity of respiratory depth was observed even in the patients who did not complain of any respiratory discomfort at the time of examination. Furthermore, it was interesting to know that this finding was seen in the patients whose respiratory complaints were not so strong, as stated later.

Sighing—

A sigh is regarded as one kind of irregularity of respiration. It is charac-

terized by the intermittent augmentation of the amplitude of the curve, although the linearity of the curve is maintained, as indicated in Fig. 4.



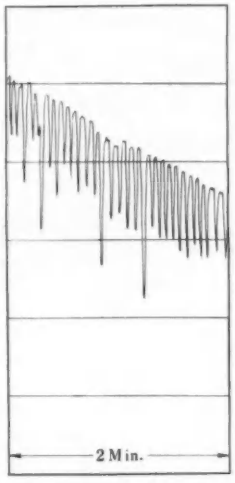


Fig. 3 (Left). Number of cases showing each grade of the irregularities of the depth of respiration.

M = Mean value of tidal volume of approximately 30 breaths

σ = Standard deviation of tidal volume

The number of cases are indicated above each column.

Fig. 4 (Right). The respiratory curve showing sigh. NCA, 30 of age, male.

This sign was observed in several cases of our NCA patients. Sometimes it was recorded at the period when the patients felt no discomfort. This fact was already described by White and Hahn[6] as one of the characteristics of NCA. They emphasized it to be useful to differentiate NCA from the organic heart diseases.

In my experience, however, it was not observed in every case and even the healthy persons had a sigh when they were fatigued or in emotional states. Accordingly, it cannot be regarded as an indisputable sign for the diagnosis.

Fluctuation of the Respiratory Level—

The slope of the respiratory curves recorded by the metabulator is usually smooth and linear. In NCA, the slope was not smooth in some cases, as indicated in Fig. 5. Christie[7] pointed out this finding as characteristic for NCA, in addition to the shallow and frequent respiration and the irregularity of its depth. These findings were, of course, not observed in all cases. Some authors[8] did not agree with his opinion that the shallow and frequent respiration is one of the characteristic findings in NCA.

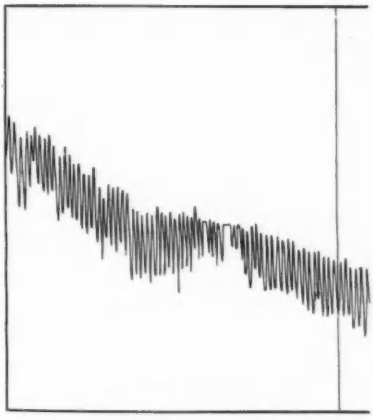


Fig. 5. The fluctuation of the respiratory level in NCA, 23 of age, female.

The fluctuation of the respiratory level may be due to the unstable state of the respiratory muscle tone. In animal experiments, the stimulation of the vagus nerve shifts the respiratory level to the inspiratory side, while the pain (for instance, stimulation of the sciatic nerve) to the expiratory side.[9] From this viewpoint, the non-linearity of the respiratory level in NCA can be attributed to the hypersensitivity to these stimuli.

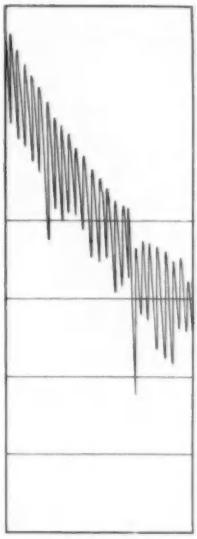
Disorder of the Respiratory Curves Caused by Stimulation—

It was often observed that the patient drew a deep breath when somebody walked around his bed or made noise during metabulator recording. Fig. 6 shows an example, in which a single deep breath was observed when such stimulation was applied. The healthy subjects did not show any reaction to the external stimuli of the same strength. This means that NCA patients are more sensitive to the environmental stimulation in comparison to the healthy. In literature, the influences of the pistol shot on the heart rate or on the respiration were investigated by Meakins and Wilson.[10] My experiments indicated that weaker stimuli than pistol shot could cause disorder of the respiratory curves. In this regard, it is suggested that the palpitation which is not felt by usual persons is perceived as discomfort in NCA. Such findings were, however, not observed in all cases. Rather few cases showed them.

These findings seem to be identical to Cohen's observation that the threshold for pain is lower in NCA.[11] Similarly, Jones[12] observed the increase in the respiratory minute volume by pain, compressing the subject's arm by the cuff of sphygmometer.

Observations in the Respiratory Function Tests—

Vital capacity: Some authors reported diminution in the vital capacity in NCA,[13] while others did not agree with them.[5] At any rate, nobody has insisted that diminution in vital capacity is a characteristic finding. My



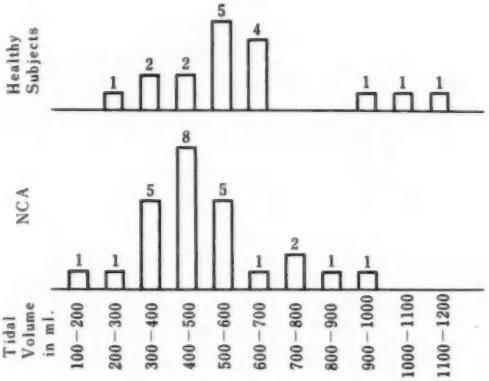


Fig. 6 (Left). The second (right-sided) deep breath was observed, when a nurse walked around the patient's bed. NCA, 21 of age, male.

Fig. 7 (Right). Tidal volume in the healthy and NCA, showing the number of cases above each column.

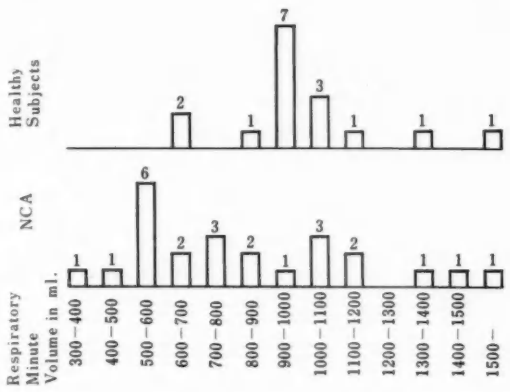
study also failed to show any demonstrable change in vital capacity.

Tidal volume: No particular findings were observed in the tidal volume, although relatively smaller values were seen in NCA than in the helathy, as shown in Fig. 7.

Respiratory minute volume: No significant difference was observed between the patients and the healthy. According to Jones and Scarisbrick,[8] the mean value of the respiratory minute volume is 10.71 L. in the normal and 10.6 L. in NCA. In my study, NCA patients showed smaller value than the healthy subjects, as seen in Fig. 8, although the difference was not statistically significant.

Ventilation equivalent: This value corresponds to the respiratory minute volume/oxygen uptake for a minute $\times 100$. The large value means the poor efficiency of respiration. The results were shown in Fig. 9. In four of my patients the value exceeded the upper normal limit. According to Knipping,[14] the normal value ranges from 1.8 to 3.6, with a mean of 2.4. All cases of the healthy subjects in my series showed a value within this range. It was suggested that the efficiency to take up oxygen is poor at least in a few cases of NCA.

Changes in the respiration after exercise: In general, the NCA patients complain of breathlessness after exercise. According to Jones and Scarisbrick,[8]



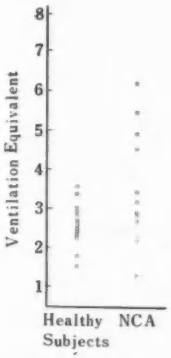


Fig. 8 (Left). Respiratory minute volume in the healthy and NCA, showing the number of cases above each column.

Fig. 9 (Right). Ventilation equivalent in the healthy and NCA.

respiratory minute volume was increased from 10.7 L. at rest to 20.5 L. after exercise in the healthy subjects, while from 10.6 L. to 27.4 L. in NCA patients. In other words, the NCA patients need more air during and after exercise. They pointed out also that the NCA patients need longer time for the return of this value to the previous level than the healthy. Cohen and White[5] also reported the higher increase in the respiratory minute volume in NCA during and after walking.

In my examination employing Master's two step test, the mean value increased from 9.7 L. at rest to 18.59 L. after exercise in thirteen cases of the healthy individuals, while 8.71 L. to 18.5 L. in sixteen cases of the NCA patients. The difference is not quite significant as that reported by Jones and Scarisbrick. But, since oxygen was used in the metabulator examination, the results cannot be compared with their data in the strict sense. The time needed for the recovery to the previous level did not differ in the healthy and NCA patients.

Discussion

It has been pointed out by many authors that most of the NCA patients have respiratory discomfort. In some cases the respiratory complaints predominate the circulatory ones. In Christie's opinion,[7] such conditions are better to be called as respiratory neurosis.

Table I shows the respiratory findings observed in my twenty-two cases of NCA. All of them have some respiratory complaints or findings. Some patients show objective respiratory findings without any respiratory complaints. In this regard, it is very valuable that the respiratory findings are

Table I. The Respiratory Findings in Neurocirculatory Asthenia

Case No.	Age	Sex	Subjective symptoms concerning respiration	Irregularity of depth of respiration (σ/M)	Sighing	Fluctuation of respiratory curves	Ventilation equivalent
1	35	f	−	+			
2	32	f	−	+	+		
3	27	f	−				
4	31	m	+				
5	25	m					
6	38	m	+		+		
7	30	m	+	+	+		
8	23	f	+	+	+		
9	20	m	−	+	+		
10	50	m	+	+	+	+	+
11	32	m	+		+		
12	23	m	−	+		+	
13	43	m	−			+	+
14	31	f	+	+			
15	41	f	−		+	+	+
16	45	m	+		+		
17	25	m	+	+	+	+	
18	20	m	+	+			
19	30	m	+	+	+	+	
20	18	m	−	+			
21	29	m	+	+	+		
22	41	f	+	+			

observed objectively in the NCA patients even at the period when they feel no discomfort. It can be said that these findings, especially that of the irregularity of the depth of breaths, are regarded as positive diagnostic criteria for NCA.

Recently, various newer drugs such as ergotamine tartrate, meprobamates, chlorpromazine, Carnigen and others have been used for the treatment of NCA. It is difficult to evaluate their effects on NCA because we have no adequate objective measures. In my opinion, this can possibly be done by comparing the irregularity of the respiratory depth.

Fig. 10 shows the value of σ/M before and after administration of Bellergal, containing belladonna, ergotamine tartrate and barbiturate. When this value was high before administration, it became lower, while the cases with normal value showed little change.

Summary

(1) The respiratory functions were investigated by metabulator in 25

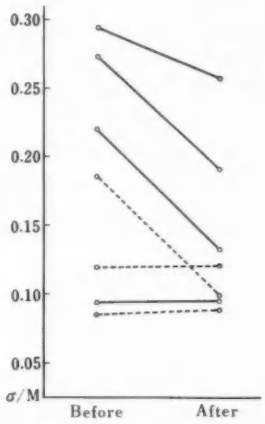


Fig. 10. The irregularity of the depth of respiration before and after administration of Bellergal.
----- after a single dose
——— after administration for a week

cases of neurocirculatory asthenia and 15 healthy subjects.

(2) The depth of respiration was irregular in NCA, while it was regular in the healthy.

(3) As an index for irregularity of the depth of respiration, the value of its standard deviation divided by the mean value of the depth in the respiratory curves may be used.

(4) The index for irregularity was significantly greater in NCA than in the healthy.

(5) The sigh was observed in some patients.

(6) The slope of respiratory curves recorded by metabulator was usually smooth and linear in the healthy. In NCA it was irregular and fluctuating.

(7) When the patient was stimulated by some methods, deepening of a breath was observed.

(8) No particular difference was observed in the tidal volume between the healthy and patients.

(9) The respiratory minute volume was a little smaller in NCA than in the healthy.

(10) In some patients, the ventilatory equivalent exceeded the upper normal limit. This means poor efficiency to take up oxygen in NCA.

(11) The augmentation of the respiratory minute volume after exercise did not differ in the healthy and patients.

(12) The above mentioned findings were seen in most cases of the patients.

(13) These findings were observed in patients who had no respiratory

discomfort or at the period when the patients had no respiratory complaints.

(14) The neurocirculatory asthenia has no specific findings to serve for its diagnosis. However, the irregularity of the depth of respiration, sighs, and higher value of the ventilation equivalent seem to be useful for the diagnostic criteria of the disease.

(15) The index of the standard deviation divided by mean value of the depth of respiration reduced after administration of Bellergal, when it was high before, and may be used for evaluation of the effects of various drugs for NCA. It may be useful also for an objective measure for the seriousness of the disease.

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Special Articles

Conceptional Changes of Electrocardiographic Theories as Developed by the Advent of the Microelectrode Technique

Toyomi SANO, M.D.*

The recent microelectrode technique enabled us to clarify the electrical activity of the single cardiac muscle fiber even in situ. Thus it revealed various relationships between this and the electrocardiogram and permitted to solve the old electrocardiographic controversies on intrinsic deflection, ventricular fibrillation and others. It also enabled us to discover various secrets of the atrioventricular conduction, including the so-called unidirectional atrioventricular conduction. According to these results, it was felt that the theories of the electrocardiography should be re-established.

The Time Relation between the Electrical Activity of Single Cardiac Muscle Fiber and the Deflections of the Electrocardiogram

The method of capillary ultramicroelectrode has awaken a new stimulus to the theory of electrocardiography. Its various theories which were believed to have been established have been reevaluated by this technique and were found to be far from being established. Because of weak points inherent in this technique such as fragility of the tip of the microelectrode, it enables us to solve the problems only partly, but on the other hand it has a great merit in supplying us with informations concerning the electrophysiology of cardiac muscle fiber directly.

First of all, the current theory of electrocardiography has been established under the concept that propagation of excitation in the ventricle or in the atrium can be pursued by electrocardiogram. But whether or not or to what extent it is possible has not been sufficiently evaluated. Recently Sodi-Pallares and associates[1] showed that the vectorcardiographic loop obtained by distant exploring and the events explored directly on the surface or within the mass of the heart had a close relation. This arouses us a question whether the direct lead electrogram may or may not show the sequence of the activation process of the heart faithfully. Namely, it is possible that even the direct lead electrogram is more or less an expression of the resultant dipole of the whole heart, distorted by the local events, or strongly

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influenced by the electrical events of the whole heart, although the parallelogram law in vector addition cannot be applied literally.

It has long been believed that the direct unipolar lead electrogram can afford us the information on the electrical events occurring in the cardiac muscle just beneath the exploring electrodes in differentiation from those in other parts. The term " intrinsic deflection " was created by Lewis,[2] having such implication. Innumerable research projects were pursued under this concept and many important conclusions were drawn until the most parts of the current theory of the electrocardiography are composed of the results thus obtained.

Previously, this concept was never doubted. It seemed to be self-evident for the old investigators but it was questioned rather recently by a few workers including Sodi-Pallares.[3] If the cardiac excitation was limited in the vicinity of and just beneath the exploring electrode, this concept may be true. The closer the cardiac elements lye to the exploring electrode, the greater influence they must give it. However, if the excitation covers greater parts of the cardiac muscle or if several cardiac parts excite with different forces simultaneously, this relation is not self-evident. There are two factors to be considered. One is the distance of the excited cardiac elements from the exploring electrode and the other is the magnitude of their electrical events that occurred, most of which is determined by number of exciting cardiac muscle fibers.

As for the former factor, when the excited cardiac elements are regarded as electric dipoles, the potential φ which the exploring electrode takes is given by the well-known equation:

$$\varphi = \frac{K\mu \cos\theta}{r^2} \qquad (1)$$

where μ is the dipole moment, r is the distance between the dipole and the electrode, θ is the angle between the dipole axis and the line connecting the dipole with the electrode and K is a constant.

Most of the pitfalls which appeared in many papers are originated from the fact that the former (distance) factor is given in square relation, therefore it is liable to be mistaken as by far the dominant factor compared with the second (number) factor. One might think that, if the distance between the exploring electrode and the cardiac muscle dipole approaches zero, the potential obtained by the former approaches infinity. But this is an illusion, because this formula postulates the distance should be far greater than the dipole distance. From the result of the actual experiment, one can never obtain so greater a potential, however close the electrode may approach the cardiac muscle fiber. Previously it was never possible to approach the cardiac muscle fiber infinitely, because, however close the conventional electrocardiographic electrode was pressed to the cardiac surface, the distance between the two remained still great. But the recent technique of the microelectrode has almost enabled us to do so. The tip of the microelectrode can be placed

just outside the cell without causing noticeable damage to the cardiac muscle fiber. Even by employing this technique we have never obtained so large potential changes, at most, more or less than 10 mV. The electrogram thus obtained was tentatively called as the surface electrogram by Woodbury *et al.*[4] Later we showed that there were no essential or marked differences in shape and size between the surface electrogram and the unipolar direct electrogram[5]. But once the microelectrode was advanced slightly and impaled into the cell, qualitatively different potential changes were obtained, amounting to about 100 mV and showing entirely different configuration which has been called as " monophasic curves " of the action potential.

Now it is clear that the distance factor has a limited magnitude, let us consider the situation in combination with the number factor. In order to get a rough but general estimation including intracavity leads, it may be better to consider the stituation like Fig. 1, namely the exploring electrode

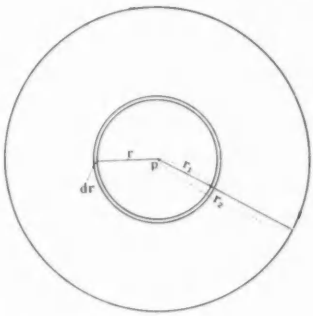

Fig. 1. See text.

P is located in a sphere. The roughest estimation is given in a special condition where θ is regarded to be the same in all the elements. Then the potential $d\varphi$ given by the excited cardiac elements at the spherical surface with a radius r is expressed by the following equation:

$$d\varphi = 4\pi r^2 dr \times \frac{K\mu\cos\theta}{r^2} = 4\pi K\mu\cos\theta\, dr \qquad (2)$$

In the equation (2), it is already seen that r^2 is crossed out. Therefore, the distance factor cannot be regarded always as to be dominant. Furthermore, the potential φ' given by all the cardiac elements outside this sphere of the radius r is given by integration of equation (2):

$$\varphi' = 4\pi K\mu\cos\theta \cdot \int_{r_1}^{r_2} dr = 4\pi K\mu\,(r_2 - r_1)\cos\theta \qquad (3)$$

Equation (3) shows that φ' becomes large to any extent as r_2 becomes large, namely, the cardiac muscle extends large, unless cos θ is zero, which is pro-

bably not the case with the cardiac syncytium. To apply the results to the usual situation where the electrode is placed outside the heart, the only thing to do for the rough estimation is to cut the sphere into several cones, resulting into no changes in the conclusion.

The above consideration is just to show that the distance factor is not necessarily far dominant. In order to treat the whole situation mathematically the factor θ should not be regarded as the same. However, here an attention should be paid for that no validity has ever been given whether mathematical methods can ultimately solve the problems or not. Therefore, in order to start again without any assumptions everything must be done experimentally.

The microelectrode technique has a great advantage that it reveals the electrical activity of the impaled cardiac muscle fiber. Taking this advantage we reexamined what point of the deflection of the unipolar direct lead electrogram corresponds to the arrival time of excitation.[6] Employing tortoise hearts in situ, the microelectrode was inserted into various points of the ventricular and auricular surface and the unipolar direct lead electrodes were placed as close as possible to them. The steepest rise of the action potential obtained by the microelectrode was compared with the deflection of the electrogram. It was found that the former corresponded to various points of the deflection between the summit of the R spike and the nadir of the S of the electrogram and no specific point of its deflection could be regarded as indicating ventricular activation time. Therefore, if the conclusions obtained by previous workers are not influenced by the time difference between the summit of the R spike and the nadir of the S according to their nature, it will not make any difference. But if they are actually influenced, the unipolar direct electrogram was thus found not to be a suitable technique to pursue the excitation propagation. Some other methods such as the microelectrode technique or more roughly the adjacent bipolar direct lead electrogram must be employed for this purpose.

Extreme examples are fibrillation and flutter, especially the former. How can it be imagined that the electrogram can reveal the excitation propagation, when the total incoordination of cardiac fibers might be anticipated? Lewis[2] and many others concluded circus movement of the excitation wave by applying direct unipolar lead electrograms. But did they not get evidences for circus movement of the excitation wave simply because the vector loops (i.e. the trace of the resultant vectors of cardiac electrical activity) form a circus? Even the total incoordination of the heart in fibrillation has not been definitely proved. It is because the same chaotic electrograms would be obtained, if the majority of the cardiac muscle fibers showed weak but regular, coordinated electric activity and numerous small islands of strong but complete irregular activity were scattered throughout the heart, for example. Although a great number of papers on fibrillation and flutter has appeared applying electrograms, no definite conclusion could be drawn thus far.

In view of such previous deficiency, we applied the microelectrode technique in the fibrillating dog ventricle in situ.[7] Comparing action potentials obtained by microelectrodes with deflections of direct unipolar lead and adjoining direct bipolar lead electrograms taken as close as possible to the impaled microelectrode, it was actually found that neither synchronism nor any other regular time relation could be found between them so far as ventricular fibrillation is concerned. These findings show that the electric activity of single cardiac muscle fiber cannot be presumed by any type of the electrocardiogram in fibrillation. Therefore, in order to decide it, two microelectrodes were inserted at points different in distance on various regions of the ventricular surface. Simultaneous recording of the two action potentials with electrocardiograms revealed that neither synchronism nor any other regular time relation existed, regardless of how ventricular fibrillation was evoked. Thus the microelectrode technique enabled us to give sounder basis for the theory of total incoordination in ventricular fibrillation than the previous works.

The Relationship of the Shape between the Electrical Activity of Single Cardiac Fiber and the Deflections of the Electrocardiograms

Many electrophysiological aspects of the cardiac cell have been clarified by the use of microelectrode since its advent. But very few studies have been undertaken on the relation between the electrical activity of the cardiac single cell and the electrocardiogram. On other cells, the fundamental electrical relations between outside and inside the cell were clarified. But it is still a matter of speculation how this relationship can be applied to the theory of electrocardiography.

Cole and Curtis,[8][9] Katz,[10] Lorente de Nó,[11] Hodgkin and Huxley,[12] Schmidt[13] and others revealed theoretically and experimentally on nerve fibers and on skeletal muscle fibers surrounded by a thin layer of a conductor, that the curves obtained extracellularly correspond to second derivatives of the action potential obtained intracellularly. Churney and his associate[14] showed that this relationship roughly held true on linear strips of tortoise atrial or ventricular muscle strip in a volume conductor. In our study a small linear strip of about 3 mm. $\times$ 10 mm. was isolated from the ventricular papillary muscle and was immersed in a volume conductor. One microelectrode was inserted into the cell of the strip, and the other microelectrode was placed outside the cell as close as possible to the first microelectrode. In general, the surface electrogram obtained by the second microelectrode was found to be roughly regarded as the second derivative of the action potential obtained by the first (Fig. 2). What is making, then, the actual electrocardiogram so different in configuration depending upon explored points in the whole heart? Is it due to a complicated sphere-like structure of the heart with the cavities and the septum, as has been believed, or, in addition, is it due to a syncytial structure of the cardiac muscle? It is important to know this,

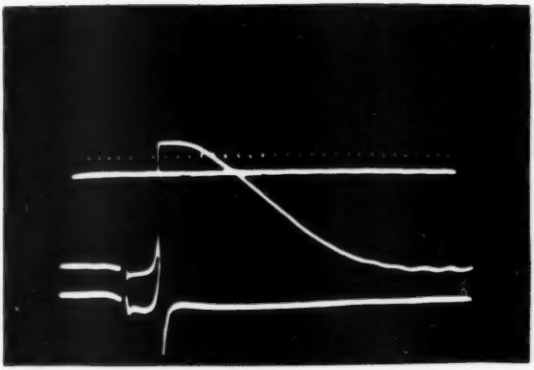

Fig. 2. An action potential (the upper tracing) and a surface electrogram (the lower tracing). Both were obtained by microelectrodes contacting side by side in a small line strip excised from a dog ventricular papillary muscle. Time marks at intervals of 10 msec.

because, if the former is the sole or a by far dominant factor, the theory of the electrocardiography can be a relatively simple one, like the current theory, starting from the second derivative theory. But, if not, the theory should be changed to a more complicated one.

In oder to find this out, a larger, flattened cardiac muscle strip of about 15 mm. × 30 mm. × 2 mm. in size was excised from the endocardial and epicardial side of various parts of the dog ventricle. A soft, thin and wett cotton swab was used as an exploring electrode for the conventional unipolar direct lead electrogram. This electrode and other two microelectrodes, one for obtaining action potentials intracellularly and the other for recording the surface electrogram extracellularly, were placed as close as possible to one another. These electrograms, especially the unipolar direct one by the cotton tipped electrode, were found to be fairly different from the second derivative of the action potential. But the most remarkable findings were the changes under the influence of some drugs such as procaine amide, quinidine, digitalis glycosides, KCl and others. Especially under procaine amide and quinidine the unipolar direct electrogram showed a bizarre form, which is far from the second derivative of the action potential, as is shown in Fig. 3. The surface electrogram by the microelectrode kept a fairly regular configuration in spite of such changes, although in the terminal stage it showed also a tendency to become slightly bizarre. Such observations were the same in both the preparation excised from the endocardial side and that from the epicardial side of the ventricle. Since the changes of the action potential were not so marked as to predict the changes of the unipolar direct electrogram, the propagation of excitation through the syncytial structure seemed to be a dominant factor to make such a bizarre form, especially when the stimulus was given artificially as in such experiments and the excitation may have been transmitted not by

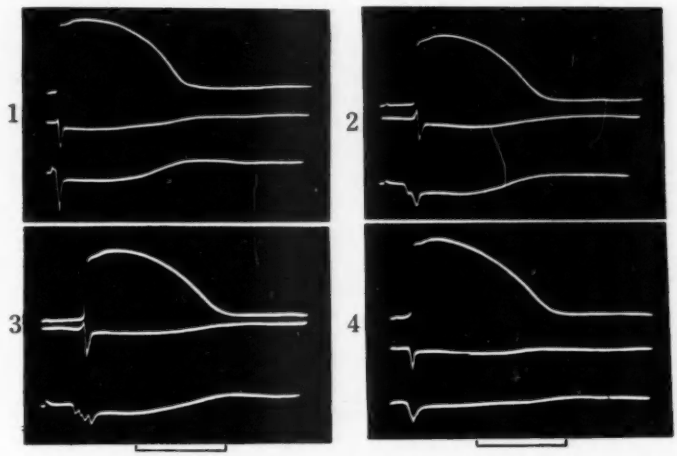

Fig. 3. The action potential (the upper tracing), the surface electrogram (the middle tracing) and the unipolar direct lead electrogram (the lower tracing) under the influence of procaine amide. An experiment with a larger muscle strip excised from a dog ventricle.

1: control; 2: immediately after adding two drops of 10% procaine amide to the impaled point of the microelectrode; 3: after 1 minute; 4: 3 minutes after renewal of the Tyrode solution.

the normal course through the specific conducting system as in situ. This series of experiments led to the following series in which the conduction time was directly measured in similar preparations from the dog ventricle, with a special attention for its directional difference.

The results of the latter experiments were reported in details elsewhere.[15] In essence the condution velocity along the longitudinal axis of the ordinary myocardial fiber was estimated as 450 to 750 mm./sec. whereas conduction vertical to the fibers as 80 to 199 mm./sec. Although these values are much smaller than the conduction velocity of Purkinje fibers, this directional difference cannot be ignored. Furthermore, this difference was shown to become more marked under the influence of some drugs, such as digitalis glycosides, quinidine, and procaine amide, and with a rise of temperature (Fig. 4).

Such a directional difference of the conduction velocity may not be possible to be revealed by the ordinary electrocardiogram. This is because the electrogram may not show any deflection, if the excitation proceeds, rapidly or slowly, in a few fibers in a given direction. Therefore, despite the fact that the excitation propagation or regression were so far reported to be in a fairly regular fashion on the basis of electrocardiographic experiments, the actual course may be much more complicated.

Mysteries of the Atrioventricular Conduction Revealed by the Microelectrode Technique

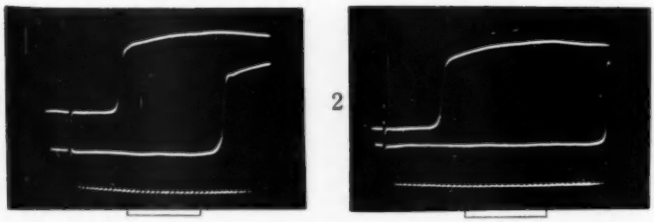

Fig. 4. The effect of digitalis on directional difference of conduction velocity. This experiment was performed to show the effect directly in this picture. Two microelectrodes were impaled in a muscle strip excised from the epicardial surface of a dog ventricle in an equal distance from the stimulating electrode, one parallel to the ordinary muscle fibers and the other vertical to them. The action potential obtained by the former is shown in the upper tracing and that by the latter in the lower tracing of each figure. Conduction time was measured by the time between the stimulus artifact and the steepest rise of the action potential in each tracing.

1: Control. Vertical conduction time is seen to be delayed.

2: After adding 2 cc. of lanatoside C in 94 cc. of the Tyrode solution.

The delay of the vertical conduction is seen to be more marked. The experiments reported in reference 15 were performed in a more accurate method employing the third microelectrode in the closest vicinity of the stimulating electrode. Time marks at intervals of 2 msec.

Another merit of the microelectrode technique in the field of the electrocardiography is that it solved many mysteries of the special conduction system. Hoffman *et al.*,[16][17] Matsuda *et al.*,[18] and we[19] found special configuration with a step-like potential in the region of the atrioventricular node and we confirmed histologically in dog hearts that the origin of this special potential is actually the nodal tissue in the region of the atrioventricular node.[20]

An action potential quite similar in shape and size with that of the atrioventricular node was found by us in the domain of the dog ventricle, i.e. in the region adjoining to the membranous portion of the interventricular septum. The origin of this was also examined histologically and was found out to be the specific junctional tissue of the bundle of His just above the bifurcation of the right and left bundle branches. As is shown in Fig. 5, no difference

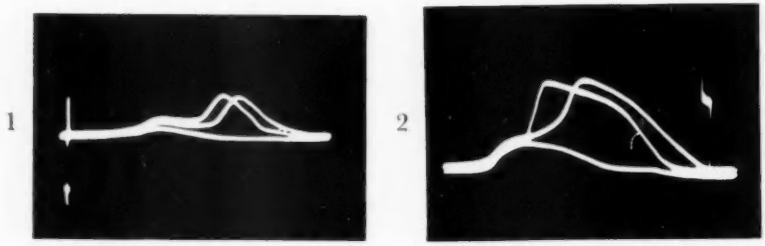

Fig. 5. The action potentials of the atrioventricular node (Fig. 5. 1) and of the bundle of His just above the bifurcation of the right and left bundle branches (Fig. 5. 2).

with the nodal action potential could be found so far as shape and size of the action potential are concerned. Namely, the action potential here was smaller than that of the ordinary atrial or ventricular muscle fibers, showing a step-like potential like that of the atrioventricular node.

In summary of the selected 18 values among 39 impalements with 31 dogs, the average resting potential was 60 mV, ranging from 40 mV to 83 mV. The action potential had an average amplitude of 58 mV, ranging from 34 mV to 77 mV, and the overshoot one of −2 mV, ranging from −12 mV to +12 mV. Duration of the action potential at the constant stimulating rate of 60 per minute was 617 msec. in average, ranging from 450 msec. to 750 msec.

What is more important, this region was found later to play an important role in the mysterious, so-called unidirectional atrioventricular conduction. Namely, it is a well-known fact that the conduction from atrium to ventricle occurs easily, whereas that from ventricle to atrium occurs only in rare instances. Although many cases of such retrograde conduction block may be ascribed to the fact that the atrial or nodal tissue is till in a refractory state, when the stimulus passes back, it was shown by us[21] that still many other cases cannot be ascribed to this reason. It is this region that was found to cause a retrograde conduction block. As was reported in detail,[21] this region was found to respond with full-sized action potential to the stimulus conducted from the atrial side, but mostly with only localized depolarization to the stimulus conducted from the ventricular side (Fig. 6 and Fig. 7).

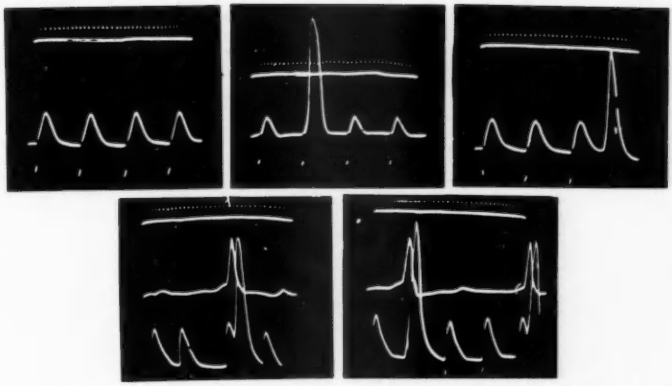

Fig. 6. The cell potential of the specific point of the bundle of His just above the bifurcation. The middle tracings in the lower row figures are the action potentials of the atrioventricular node. The stimulating electrode was placed in the ventricle. Only localized depolarization is seen usually after the stimulating artifacts, indicating retrograde conduction block, whereas full-sized action potentials are seen in sequence of the nodal action potentials, indicating the presence of normal orthograde conduction. Time marks at intervals of 100 msec.

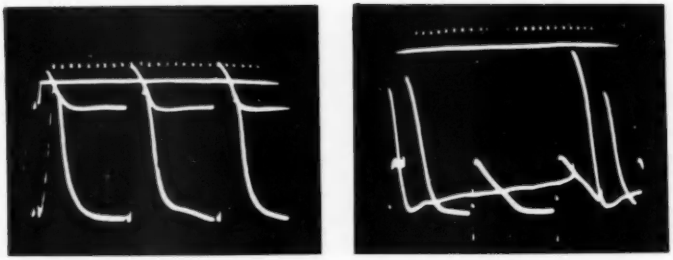

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Fig. 7. Action potentials from the atrioventricular node or its vicinity (the upper tracing) and those from the specific point of the bundle of His above the bifurcation (the lower tracing). In 1 the electrical stimulation was applied to the atrium. Full-sized action potentials are seen in the lower tracing, indicating the presence of the orthograde conduction. In 2 the stimulation was applied to the ventricle. Only localized depolarization is seen after stimulating artifacts except for the two full-sized action potentials in sequence of those of the upper tracing, indicating a retrograde conduction block. Time marks at intervals of 100 msec.

In the close vicinity of the region in the ventricle two types of action potential were obtained, both of which were of transitional shape and size. Both had relatively smaller action potentials with slower rising velocity and with little plateau. The first type was obtained distal to the retrograde conduction block point and responded to ventricular stimuli always with full-sized action potentials, resembling the response of the ordinary ventricular muscle fibers. The second type was obtained proximal to the retrograde conduction block point and did not respond to ventricular stimuli, but responded to atrial stimuli or showed spontaneous activity, in spite of the fact that its origin belonged to the domain of the ventricle. In the summary of the selected 14 values among 42 impalements in 28 dogs, the average values of resting potential, action potential and overshoot of the first type were 60 mV (ranging from 37 mV to 72 mV), 59 mV (34 mV$\sim$74 mV) and -1 mV (-18 mV$\sim+12$ mV), respectively. Summarizing the selected 6 values among 25 impalements in 21 dogs, those of the second type were 56 mV (42 mV$\sim$75 mV), 60mV (45 mV$\sim$88 mV) and 4 mV (-5 mV$\sim+13$ mV), respectively. Duration of the action potential at the constant stimulating rate of 60 per minute was 517 msec. in average, ranging from 250 msec. to 650 msec. in the first type and was 628 msec. in average, ranging from 430 msec. to 750 msec. in the second type, respectively.

Such nature of the first and second type of the cell potential supported the above-mentioned mechanism of the retrograde conduction block in the presence of normal orthograde conduction.

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Theoretical Consideration on Plasma Volume Determination

Atsuo NAKANISHI, M.D.

From the results of experiment in which the disappearance curve was observed for 8 hours or longer after the dye injection, a theory of multiple volume compartments system has been derived, assuming that dye moves in the plasma according to dye concentration difference between various compartments. It seems to be then that, even if the dilution curve had been exponential, it would not represent the true disappearance curve seen after the uniform mixing of dye with plasma. This assumption was evidently proven in the present study of the dilution curve covering a period of 10 minutes to 1–2 hours of patients with congestive heart failure.

IN recent years, the method of plasma volume determination, using the blue azo dye " T-1824," originated by Gregersen and his associates[1] and later applied for clinical use by Gibson and Evans[2] has been used commonly. The method of calculation for this plasma volume determination depends upon the amount of the dye injected and its concentration at the time when all the injected dye was assumed to be uniformly mixed with the blood stream. To obtain such a dye concentration, several extrapolation methods from a certain portion of T-1824 time-concentration curve (or dilution curve) have been advocated. But the values so determined cast some doubt upon whether they actually indicate the circulating plasma volume or total plasma volume. To answer this question, in 1951, the author has already reported a hypothesis derived by analysis of the factors shaping the T-1824 time-concentration curve.[3] In this paper, the author intends, therefore, to introduce both this hypothesis and results[4] developed later from it to the readers for the explanation of the significance of values of plasma volume. The first step to understand this hypothesis clearly is to know the causes by which the concentration of dye injected into the blood stream is decreased with the time.

Dilution Process after the Dye Injection—

Dye mixing with blood stream: It is well known that when samples are taken at 1 to 4 minute intervals over a period of 30 minutes or longer after the injection of the dye in normal subjects, the dye concentration of successive samples reaches the peak within 10 minutes. This is followed by a rapid fall of the dye concentration at first, then a gradual decrease at about a constant rate occurs. According to Gibson and Evans,[2] the initial rapid fall in con-

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centration was considered to be due to mixing of dye with the blood stream, and this portion of the time-concentration curves was termed as the mixing curve, and the subsequent portion in which the fall in the concentration is gradual and constant, was considered to be due to the removal of the dye from the blood stream principally by phagocytic function of the reticulo-endothelial system and designated as the disappearance slope. The tangent point of these two curves was called " mixing time." The mixing time in normal individual was reported seven and half minutes by Gibson and Evans,[2] 9 minutes by Gregersen[5] and in the dog 4 to 6 minutes by Miller,[6] and within 5 minutes by Gilder[7] and Lawson.[8]

To confirm these data that complete mixing is achieved within 10 minutes after dye injection in man, hepatic vein catheterization was made to obtain simultaneous dye concentration curves of hepatic and antecubital veins. As shown in Table I,[4] a total of 39 subjects consisting of 11 normal persons, 18

Table I. Comparison of Plasma Concentrations of T-1824 in the Peripheral Vein and the Hepatic Vein

Group	No. of cases	No. with agreement with less than 5% of experimental error limits		No. without agreement at 30 min. or more	No. with agreement with less than 3% of experimental error limits		No. without agreement at 30 min. or more
		within 10 minutes	in a period of 10 to 30 min.		within 10 minutes	in a period of 10 to 30 min.	
Normal	11	3	6	2	2	7	2
Liver disease	18	2	4	12	0	6	12
Other disease	10	2	8	0	1	7	2
Total	39	7	18	14	3	20	16
		25			23		

Total cases showed higher T-1824 plasma concentration in the peripheral vein.

patients with liver diseases and 10 patients with diseases other than circulatory disturbances were examined. With an error of less than 5%, 7 cases of these had the same concentration in the two veins within 10 minutes after the injection of dye, 18 had the same concentration in a period of 10 to 30 minutes, and the remaining 14 had always higher concentration in the antecubital vein than in the hepatic vein even after 30 minutes. It may be inferred therefore, that mixing is not always completed in 30 minutes even for the subjects without hemodynamic disturbances.

Disappearance of dye from the blood stream: The removal of the dye from the blood is mainly by phagocytic action of reticulo-endothelial system[9] or staining in tissues. It also appears in the lymph[10][11] and bile.[11] According to the extraction method, it may be found even in the urine.[12] In thoracic lymph the dye appeared 15 to 30 minutes after the administration of dye,

concentration of which increased gradually, amounting to 20 to 40% of the plasma level in 2 hours. This observation was confirmed later by Schultz[13] in dogs employing the labelled albumin which has been widely applied for estimation of the plasma volume. From these observations, the possibility can not be denied that as the lymph flow is too slow, the dye may have been already removed from the blood stream earlier than 10 minutes. In cervical lymph, the dye also appeared in a similar pattern to that of the thoracic duct, but its concentration was one-half of that of the thoracic duct.[10] Therefore, it is evident that a total amount of dye removed into the lymph was not small in quantity in spite of its low concentration in the lymph. In addition, it has been demonstrated that the dye appeared in the bile in 30 minutes, concentration of which reached the maximum at 60 to 90 minutes, and then decreased gradually parallel with that of the plasma. If the dye was injected intravenously in succession, the dye level of bile rose in accordance with the plasma level.[11] It was already mentioned that even in the urine the dye could be detected when the extraction method is employed. It is also well known that analogous dye to T-1824, congo red, is excreted into urine in large quantities in patients with amyloidosis and those with nephrosis.[14] Fig. 1. shows that the considerably large quantity of T-1824 dye was excreted

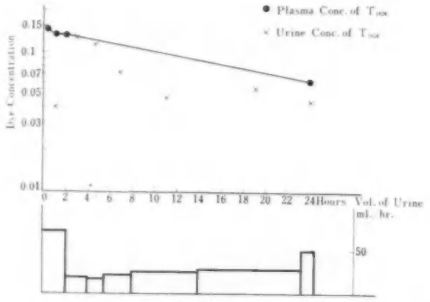


Fig. 1. Appearance of T-1824 in the urine of a patient with nephrosis.

in the urine of a patient with nephrosis, and its concentration is almost equal to the plasma level at a period of 2 to 4 hours after intravenous administration. In summary, there is reason enough to assume that the phase of the disappearance slope indicates not only disappearance but also mixing of the dye from or with the blood stream.

Extrapolation Method of the Disappearance Slope—

Extrapolation method is the means by which a dye concentration is obtained assuming all the injected dye were completely mixed with the circulating blood without loss of any dye. In practice, this method was done by extending the disappearance slope backward to the time of dye injection.

Calculation of the plasma volume based upon the extrapolation method

was first suggested by Erlanger.[15] Sunderman[16] extrapolated with a straight line from the values of the dye concentration at 30-, 60-, and 90-minutes, Gibson and Evans[2] extrapolated from the linear portion of disappearance slope by a straight line, and Gregersen[1] and Price[17] extrapolated with exponential curve. However, Hahn and his associates[18] described that the time-concentration curve could be divided into 3 phases when the logarithm of the plasma concentration of the dye was plotted against time. Miller,[6] likewise, divided the time-concentration curve into 3 phases and obtained the plasma volume by extrapolating the 2nd phase in an exponential manner. The fact that various extrapolation methods have been advocated by several investigators means evidently that the mixing and disappearance portions of the time-concentration curve blend so gradually that it is difficult to decide exactly at what point the disappearance curve begins; that "disappearance curve," strictly speaking, seems to be a straight line neither on a linear nor semilogarithmic plot.

Theoretical Analysis of Disappearance Curve—

To elucidate the complexity of the disappearance curve, the experiments were done by tracing the time-concentration curves of the dye precisely up to 30–100 hours. It was found that in 17 normal individual, 23 dogs, 31 rabbits and 24 cardiacs with or without congestive heart failure, the curve observed from 10 minutes to 1–2 hours after intravenous injection of the dye was expressed as one exponential curve with less than 5% of error limits. Whereas it was found that the curve observed from 10 minutes to 7–8 hours was expressed as a sum of two exponential curves, and in one case of a dog and a rabbit, that taken from 10 minutes up to 30–100 hours as a sum of three exponential curves. Therefore, the disappearance curve was summarized mathematically as the following experimental equation:

$$C_t = \sum_{i=1}^{n} K_i e^{-x_i t} \qquad (1)$$

where C_t is the concentration of the dye at any time, t; K_i and x_i are constants, n is 1, 2, or 3.

The same formula as equation (1)* was derived theoretically by the author from an assumption that the plasma of volume V was a system consisting of n compartments separated by boundaries from one another, according to the degree of time required for the plasma to be uniformly mixed with the dye. And it was conculuded that the disappearance curve was by no means both experimentally and theoretically either a straight line or a simple one exponential curve. Based on this theory, the dye concentration at the time of injection, C_{t_0}, is given by setting $t=0$ in equation (1). In the special case of $n=2$, not only plasma volume V can be calculated, but also the volume of 2 compartments: the volume of rapidly circulating plasma, V_1, and that of sluggishly moving or stagnant one, V_2. In normal subjects the ratio of V_1 to V was

* The derivation of this and subsequent equations will be found in Appendix.

91±3%, and in patients with congestive heart failure, it was 83–61%. These results were interpreted to show a fact that the latter had more sluggish plasma than the former. Here, the sluggishly moving plasma denoted the slowly moving and stationary plasma in the minute vessels. However, in such cases, it was necessary to trace the time-concentration curve as long as 7 to 8 hours. Because of this handicap, equation (1) is usually employed as n=1. In this case, equation (1) becomes:

$$C_1 = C_{10} e^{-k'_o t} \qquad (2)$$

therefore,

$$\text{plasma volume } V = \frac{M}{C_{10}}$$

where C_1 is the concentration of the dye at any time, t, C_{10} is the concentration of the dye at the time of the injection, M is amount of the injected dye, and k'_o is the disappearance coefficient.

Analysis of the Disappearance Coefficient k'_o—

If the plasma with a definite concentration of the dye flows without friction, and flows repeatedly at an uniform flow rate in the loop-pipe of volume V, and the dye leaks out from a special plane supposed to be in the loop-pipe, the rate of decrease in the number of units of dye, q_1, in the loop-pipe at any time, t, is dependent upon flow rate F and the concentration C_1 at the time of t. Therefore,

$$\frac{dq_1}{dt} = -\alpha C_1 F \qquad (3)$$

where α is constant relating to the efficiency of the plane. Dividing both sides of equation (3) by V, the rate of change in concentration is given as:

$$\frac{dC_1}{dt} = -\alpha \frac{F}{V} C_1$$

which on integration

$$C_1 = C_{10} e^{-\alpha \frac{F}{V} t} \qquad (3')$$

where C_{10} is the concentration before the leakage of the dye.

From equations (2) and (3'), it follows that, if the equation (2) expresses the "disappearance curve due to constant rate of concentration decrease inscribed solely to the removal of the dye from blood stream occurring after the completion of uniform mixing with plasma of flow rate F, disappearance coefficient k'_o should be proportional to the ratio of plasma flow, F, to plasma volume, V, or to the ratio of blood flow to blood volume.

For practical purposes, cardiac output may probably be applied to the blood flow, since the greater part of injected dye is mixed with the blood stream into the heart. Thus, in 5 normal individuals and 11 cases with various

diseases including 6 with congestive heart failure due to valvular lesions, two with pulmonary emphysema, and one case of thyrotoxicosis, nephrosis and splenomegaly, cardiac output was estimated by using the cardiac catheterization technic, and blood volume was determined from the value of plasma volume and hematocrit. The value of plasma volume was calculated by extrapolating the from 10-minute to 1–2 hour time-concentration curve of T-1824 as one exponential curve. As seen in Fig. 2, the negative correlation between the disappearance coefficient and the ratio of cardiac output to blood volume was small ($r=0.42$), but was statistically significant. This was an unexpected result, since it would have been positive.

In Fig. 2, it appears to show that cardiac cases with failure have higher values of k'_0 than that of normals. This relation was also presented at different occasion in a great number of cases[3] (Fig. 3). This finding is illustrated in

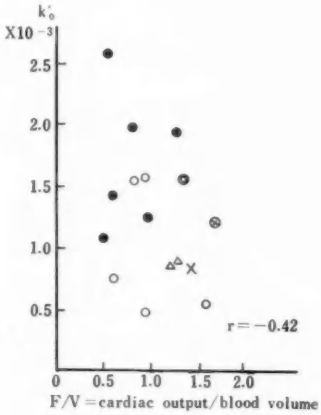


Fig. 2. Correlation of disappearance coefficient k'_0 (ordinate) to cardiac output blood volume ratio (abscissa) in normal subject ○ and in patients with congestive heart failure ●, with thyrotoxicosis ◎, with pulmonary emphysema △, with nephrosis ×, and with splenomegaly ⊕.

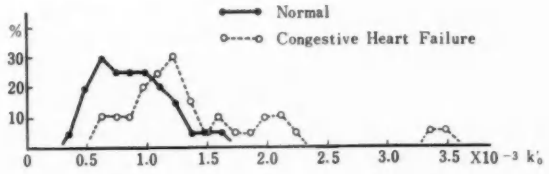
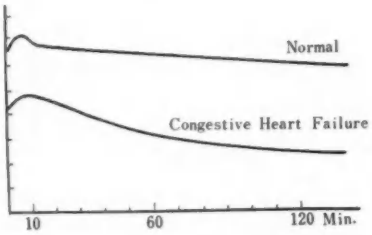


Fig. 3. Frequency distribution of values for k'_0 in normal subjects and in patients with congestive heart failure.

Fig. 4 as a schematic drawing. While the dilution curves of normals decrease rapidly, as the initial mixing for 10–20 minutes, and then fall gradually at

nearly a constant slow rate of decrease, those of cardiac cases decrease at a rapid rate corresponding to that of initial mixing of normals for as long as 1–2 hours, indicating that the mixing which occurs early in the normals will continue as long as 1–2 hours in cardiac cases.

As illustrated in Fig. 5, in normal subjects, mixing with the stagnant



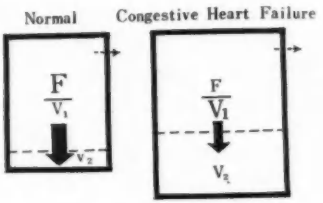


Fig. 4 (Left). Schematic representation of the dilution curve of normal subjects and of patients with congestive heart failure. Ordinate, concentration of dye; and abscissa, time in minutes.

Fig. 5 (Right). Schematic representation of 2-compartment system in a normal subject and patient with congestive heart failure. V_1, volume of rapid circulating plasma; V_2, volume of stagnant plasma; and F, minute volume of plasma.

plasma occurs so early, because of its relatively small volume, that k'_o nears the " true " disappearance coefficient seen after the uniform mixing with all the plasma in the body, which should be proportional to the rate of cardiac output to the blood volume. On the other hand, in cases with congestive heart failure, mixing is taking place so late up to 1–2 hours, because of lower cardiac output and large volume of stagnant plasma, that k'_o becomes to express not only the disappearance of the dye to the outside of the blood vessels, but the dye mixing with stagnant plasma.

For these reasons, k'_o becomes larger in the cases with congestive heart failure than that in normals, notwithstanding that F/V is smaller as compared to normals. In retrospect, it was an error to take dilution curve covering from 10 minutes up to 1–2 hours as " true " disappearance curve, on account of that it had been possible to express it as one exponential curve with less than 5% of experimental error. If the observation time would have been for 7–8 hours, and whereby the dilution curve would have been decomposed into 2 exponential components, and if the corresponding exponential curves of normals and cases with congestive heart failure were compared, such an error should not have happened.

That k'_o increases with the rise in F/V, was proven in normal subjects by the fact that, when F/V increased 4 times by epinephrine injection as compared with that in the control period, k'_o increased 3 times (Fig. 6).

Change in Disappearance Coefficient k'_o *at the Repeated Determinations of Plasma Volume—*

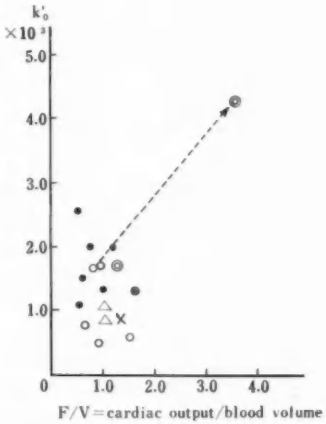


Fig. 6. The change in disappearance coefficient k'_o and cardiac output/blood volume after the administration of epinephrine.

In 4 men and 5 dogs, the second dose of the dye in the same amount was injected 1 hour after the first injection. In each case, plasma volume was determined by extrapolation of dilution curve covering a period of 10 minutes to 1 hour. All cases except 1 human subject showed the identical values of plasma volume with less than 5% of error, while k'_o was smaller in the second determination than the initial in all cases except 2 dogs.

Since k'_o of the second dilution curve is, as described below, dependent upon k'_o of the first dilution curve and the time of the second injection, it was a natural result for the second k'_o to be smaller than the initial k'_o under the conditions examined. Therefore, it must be considered carefully to estimate the function of the reticulo-endothelial system from the change in k'_o as already reported.[19][20]

Fig. 7 shows the case where the first 1 hour part of dilution curve observed up to 2 hours was superimposed on the subsequent one hour part, assuming that the second injection was done with the same amount of dye. The rate of concentration decrease of the composed curve was smaller than that of the first part of the original curve. This indicates that the degree of mixing with stagnant plasma is different according to the portions (or phases) of one exponential curve; in the last half portion of this, the mixing is performed more completely than in the first portion. Therefore, the rate of concentration decrease of the composed curve becomes smaller by influence of the latter half part of original curve.

Relation between k'_o *and Plasma Protein*—

Rossiter[21] has emphasized earlier that k'_o was in close relation with albumin concentration in plasma, on the ground that T-1824 combines firmly with the plasma albumin. However, the author[4] could not agree with his

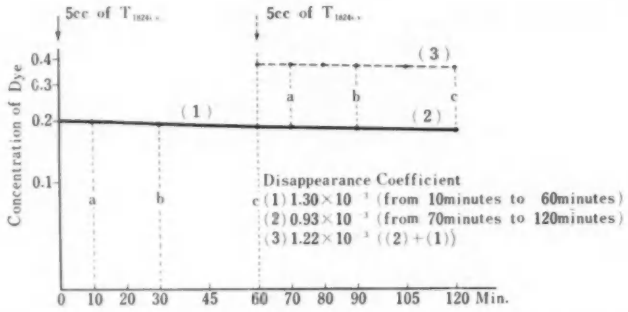


Fig. 7. Comparison of value for the disappearance coefficient k'_0 observed after the second injection with that observed after the initial injection. The second injection was supposed to have been done with the same dose at one hour after the initial injection.

assertion by the results obtained from 16 cases of human being examined, that k'_0 has no statistically significant correlation with plasma total protein ($r=-0.17$), plasma albumin ($r=+0.001$), and plasma globulin concentrations ($r=-0.05$), respectively.

It has been also reported that one molecule of albumin bound with seventy molecules of T-1824.[22] According to Rawson,[23] the dosage usually used for plasma volume determination, 20–15 mg. of T-1824, was said to combine with albumin contained in 89–67 cc. of plasma. In addition, the same value of plasma volume was given even when a twenty-fold dye was administered.[20] These indicate that k'_0 has almost no relationship to the concentration of plasma albumin with the dosage usually employed.

In summary, it was found that the dilution curve covering a period of 10 minutes to 1–2 hours showed the disappearance of the dye from the blood stream and mixing of the dye with the stagnant plasma, even if it presents one exponential curve within the experimental error limits. Consequently, extrapolation of such a dilution curve as one exponential curve comes to measure the volume of the circulating plasma including a part of the stagnant plasma. It was due to the false logic consideration that the sum of at least 2 different exponential curves was expressed as one mean exponential curve. Accordingly, the volume of circulating plasma thus measured should be deemed as the volume of "space." Even though circulating plasma volume is measured by dividing one exponential curve into two different types of exponential curve, it shows the volume of "space" after all.

Comparison of the Plasma Volume Calculated from the Ten-minute Sample with the Results Obtained by Extrapolation of the Dilution Curve as One Exponential Curve—

When the plasma volume calculated from the 10-minute sample, by the commonly used method of Gregersen, was compared with the more accurate values obtained by one exponential extrapolation of the dilution curve in a total of 41 cases including normal individual and patients with various dis-

Table II. Comparison of Values for Plasma Volume by Gregersen's 10-minute Method and by Extrapolation Method of One Exponential Curve

	Percent change from the extrapolated values						
	Increase				Decrease		
	more 5%	3%	1%	−1%	−3%	−5%	less
No. of cases	3	9	19	7	2		1
Average	+0.01%						

cases, these two instances almost agreed within the experimental error limits, so far as the time of onset of observed curves was limitted to 10 minutes after dye injection (Table II). Therefore, Gregersen's method may be utilized as a simple method in place of the one exponential method, however this method does not represent the true values of total plasma volume, but the values of " space " at 10 minutes.

Summary

(1) A theory has been derived from analysis of the factors shaping the dilution curve in the multiple volume compartments, assuming that injected dye moves in the plasma, according to its concentration difference between the compartments.

(2) From the theoretical analysis of disappearance coefficient, it has been clarified that a) dilution process during a period of 10 minutes to 1–2 hours was governed by the mixing of dye with the plasma and removal of dye from the blood stream, b) during this period mixing was performed completely in a great number of normal individuals, whereas mixing was still in process in some patients with congestive heart failure, c) plasma volume estimated by one exponential extrapolation of dilution curve covering a period of 10 minutes to 1–2 hours was considered as the values of " space," and d) the 10-minute method of Gregersen is useful as a simple method, but the values thus obtained do not represent the true plasma volume.

(3) This theory offers an actual determination of plasma volume and the stagnant plasma volume. This appeared to be very useful clinically in case of congestive heart failure.

Appendix: Derivation of Equations

As shown in Fig. 8, it was assumed that a system of the total plasma of volume V could be divided into n-compartment of volume, V_1, V_2, ... and V_n, by boundaries, according to the degree of time for the plasma to be uniformly mixed with the dye. If the amount of the dye, M, injected into the plasma of volume V_1 transfers from V_1 to V_2, from V_2 to V_3, . . . and from V_{n-1} to V_n successively and is lost, in part,

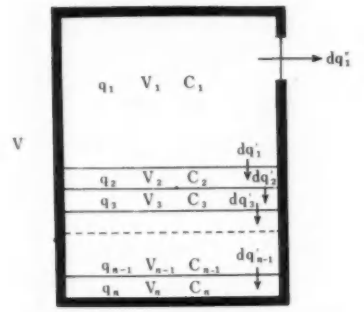


Fig. 8. Schematic representation of the n-compartment system of the total plasma of volume, V.

from the blood vessels of volume V_1, mainly by the function of the reticulo-endothelial system, under the assumption that a number of units of the dye transfers by the concentration difference of two compartments facing the boundary and the dye contents are homogenous in each chamber, the transfer rate of a number of units of dye from each chamber at any time, t, is given by

$$\left.\begin{aligned}
\frac{dq''_1}{dt} &= C_1 k_o \\
\frac{dq'_1}{dt} &= (C_1 - C_2) k_1 \\
\frac{dq'_2}{dt} &= (C_2 - C_3) k_2 \\
&\vdots \\
\frac{dq'_{n-1}}{dt} &= (C_{n-1} - C_n) k_{n-1}
\end{aligned}\right\} \quad (1)$$

where dq''_1 is a number of units of dye transferred from V_1 to outside; dq'_1, from V_1 to V_2; dq'_2, from V_2 to V_3; ... and dq'_{n-1}, from V_{n-1} to V_n; and C_1, C_2, C_3, ... C_{n-1} and C_n are the concentrations of the dye in the compartments of V_1, V_2, V_3, ... $V_{n-1}$and V_n, respectively. Here, k_o, k_1, k_2, ... and k_{n-1} are considered to be related to the character of each boundary and plasma flow in V_1, V_2, V_3, ... and V_{n-1}, respectively. The rates of change in the number of units of dye, q_1, q_2, q_3, ... q_{n-1}, and q_n, remaining in each chamber at any time t are expressed as:

$$\left.\begin{aligned}
-\frac{dq_1}{dt} &= \frac{dq''_1}{dt} + \frac{dq'_1}{dt} \\
\frac{dq_2}{dt} &= \frac{dq'_1}{dt} - \frac{dq'_2}{dt} \\
\frac{dq_3}{dt} &= \frac{dq'_2}{dt} - \frac{dq'_3}{dt} \\
&\vdots \\
\frac{dq_n}{dt} &= \frac{dq'_{n-1}}{dt}
\end{aligned}\right\} \quad (2)$$

Combining equations (1) and (2), and dividing equation (2) by V_1, V_2, V_3, . . . and V_n, to get the change in concentration per unit of time, we have:

$$\left.\begin{aligned}
\frac{dC_1}{dt} &= \{-C_1k_o-(C_1-C_2)k_1\}/V_1 \\
\frac{dC_2}{dt} &= \{(C_1-C_2)k_1-(C_2-C_3)k_2\}/V_2 \\
\frac{dC_3}{dt} &= \{(C_2-C_3)k_2-(C_3-C_4)k_3\}/V_3 \\
&\vdots \\
\frac{dC_n}{dt} &= (C_{n-1}-C_n)k_{n-1}/V_n
\end{aligned}\right\} \quad (3)$$

As equation (3) gives linear differential equation of the n th order with constant coefficients, general solution for C_1 is

$$C_1=\sum_{i=1}^{n} K_ie^{-xit} \qquad (4)$$

where K_i is the constant of integration. This formula (4) is identical with equation (1) in the text.
Under the condition that t=o, equation (4) becomes:

$$C_1=K_1+K_2+ \ . \ . \ . \ +K_n$$

Setting C_{10} instead of C_1,

$$\text{plasma volume } V_1=\frac{M}{C_{10}}$$

For the special case of n=2, when the total plasma of volume V, was divided into the circulating plasma of volume V_1 and the sluggish one of volume V_2, equation (3) becomes

$$\left.\begin{aligned}
\frac{dC_1}{dt} &= \{-C_1k_o-(C_1-C_2)k_1\}/V_1 \\
\frac{dC_2}{dt} &= (C_1-C_2)k_1/V_2
\end{aligned}\right\} \quad (5)$$

Setting $k_o/V_1=k'_o$ (disappearance coefficient) and $k_1/V_2=k'_1$, equation (5) becomes:

$$\left.\begin{aligned}
\frac{dC_1}{dt} &= -V_2(C_1-C_2)k'_1/V_1-C_1k'_o \\
\frac{dC_2}{dt} &= (C_1-C_2)k'_1
\end{aligned}\right\} \quad (6)$$

Solving for C_1

$$\frac{d^2C_1}{dt^2}+\frac{dC_1}{dt}\left\{k'_1\frac{V_1+V_2}{V_1}+k'_o\right\}+k'_ok'_1C_1=0$$

On integration, general solution for C_1 is given by

$$C_1=K_1e^{+x_1t}+K_2e^{+x_2t} \qquad (7)$$

Here,

$$\left.\begin{aligned} x_1 &= -\frac{1}{2}\left(k'_1\frac{V_1+V_2}{V_1}+k'_o\right)-\sqrt{\frac{1}{4}\left(k'_1\frac{V_1+V_2}{V_1}+k'_o\right)^2-k'_1k'_o} \\ x_2 &= -\frac{1}{2}\left(k'_1\frac{V_1+V_2}{V_1}+k'_o\right)+\sqrt{\frac{1}{4}\left(k'_1\frac{V_1+V_2}{V_1}+k'_o\right)^2-k'_1k'_o} \end{aligned}\right\} \quad (8)$$

Equation (7) shows that the concentration of the circulating plasma, C_1, at any time, t, is expressed as a sum of two exponential curves. Circulating plasma volume V_1 is likewise gained from

$$V_1=\frac{M}{C_{10}} \quad (9)$$

where M is the amount of injected dye, and C_{10} is dye concentration at the time when t=o in equation (7). Differentiation of equation (7) gives

$$\frac{dC_1}{dt}=x_1K_1e^{+x_1t}+x_2K_2e^{+x_2t} \quad (10)$$

When t=o in the combination of equations (6), (7) and (10), $C_1=C_{10}$ and $C_2=o$

$$\left.\begin{aligned} K_1+K_2&=C_{10} \\ x_1K_1+x_2K_2&=-C_{10}(k'_1V_2/V_1+k'_o) \end{aligned}\right\} \quad (11)$$

From the equation (11),

$$\left.\begin{aligned} K_1&=C_{10}\,(k'_1V_2/V_1+k'_o+x_2)/(x_2-x_1) \\ K_2&=C_{10}\,(k'_1V_2/V_1+k'_o+x_1)/(x_1-x_2) \end{aligned}\right\} \quad (12)$$

By using equations (11), (12), and (9), V_1/V_2 or V_1/V can be calculated.
For the special case of n=1 where dye is lost from the blood stream after the completion of uniform mixing, equation (3) becomes

$$\frac{dC_1}{dt}=-C_1k_o/V_1=-k'_oC_1$$

which, on integration, gives

$$C_1=K_1e^{-k'_ot}$$

To evaluate K_1, we have the condition that when t=0, $C_1=C_{10}$, which gives

$$C_1=C_{10}e^{-k'_ot} \quad (13)$$

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Case Reports

Congenital Aneurysm of the Right Coronary Sinus of Valsalva with Rupture into the Left Ventricle

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ANEURYSM of the sinus of Valsalva is a rare abnormality. Since the first description by Thurmann in 1840, about 50 cases have been reported. Among these, a case of an aneurysm of the sinus of Valsalva which ruptured into the left ventricle was described by Warthen[1] in 1949.

The purpose of this paper is to present a case of a congenital aneurysm of the right coronary sinus of Valsalva which ruptured into the left ventricle, and to discuss this abnormality.

Case Report

A 52-year-old man was admitted to the Tokyo University Hospital on November 24, 1958, with complaints of "exertional dyspnea and palpitation" for 3 months.

Patient had been well till September 5, 1958, when he experienced severe dyspnea associated with precordial pain. At the time of this occurrence patient was running fast to get on a train. On September 8, 1958, he entered another hospital where a diagnosis of the combined valvular disease was made. He was treated with salt restriction and digitalization. However, against a doctor's advice he discharged himself from the hospital. After a short period of time, especially paroxysmal nocturnal dyspnea increasingly became worse. At the same time, he noted the shortness of breath on walking or climbing stairs and had a productive cough with a white foamy sputum. On November 24, 1958, he was admitted to the Tokyo University Hospital. He had no history of syphilis or rheumatic fever. Family history was noncontributory.

Physical Examination: No cyanosis present. Blood pressure was 150/0 mm. Hg; pulse regular and rate 100 per minute; respiration regular and 20 per minute; temperature 98°F. There was no periorbital edema and conjunctival pallor. Pupils reacted normally to light and the fundi appeared normal. Tonsils were small and normal in appearance. Neck veins were moderately distended and pulsating in sitting position. Venous pressure was 120 mm. in water. Carotid and sub-

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clavian arteries pulsated vigorously. No mass or node was palpable in the neck. The examination of the lung revealed moist rales and dullness at the right lung base. The cardiac apical beat was forceful and localized to an area in the left fifth intercostal space 2 cm. lateral to the midclavicular line. The right heart border was percussed 1 cm. lateral to the sternum. The left heart border was percussed 3 cm. lateral to the left midclavicular line. On auscultation there were a soft systolic and an early high-pitched diastolic murmur of maximum intensity in third left intercostal space in the parasternal line. These murmurs were transmitted along the left sternal border to the apex. At the apex, a weak systolic and a diastolic murmur were heard. The machinery continous murmur was not heard. The liver was palpable two finger-breadths below the right costal margin and slightly tender. The spleen was not palpable. No abdominal masses were palpable. There was no ascites and no edema. Neurologic examination was normal.

Laboratory Data: Urinalysis; specific gravity 1.025, yellowish colored, albumin trace, sugar negative, bile and urobilinogen negative, sediment negative.

Hemogram; hemoglobin 70%, R.B.C. 385 millions, W.B.C. 5800 with an essentially normal differential, platelet 16.9 millions, sedimentation rate 60 mm. per hour. Wassermann reaction was negative.

Blood chemistry; blood non-protein nitrogen 26.5 mg./100 ml., total cholesterol 178 mg./100ml. Electrolytes were all within normal range, total serum protein 8.0 Gm./100 ml. Serum albumin and globulin ratio was within normal limits. C-reactive protein was two plus.

Roentgenogram; P-A chest X-ray (Fig. 1) revealed cardiac enlargement with

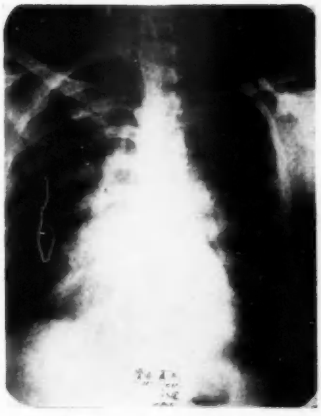
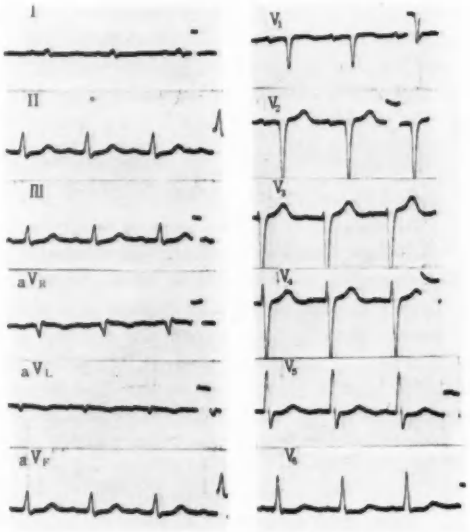


Fig. 1. Chest X-ray.

the prominence of the left ventricular contour. Cardiac fluoroscopy demonstrated enlargement of the left ventricle, left atrium and right ventricle.

Electrocardiogram (Fig. 2) was suggestive of left ventricular hypertrophy. There was slight depression of the ST segment in leads I, II, aV_F, V_5 and V_6. On the phonocardiogram (Fig. 3), a high-pitched decrescendo diastolic murmur immediately following the second sound and an early systolic murmur with a low amplitude



Nov. 27, 1958

Fig. 2. Electrocardiogram.

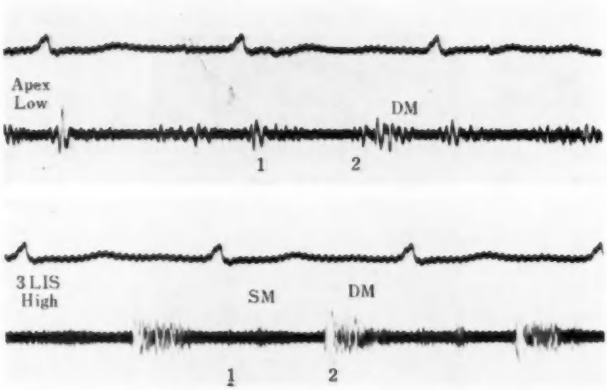


Fig. 3. Phonocardiogram in the apex and the third left intercostal space.

were recorded at the third left intercostal space. A low-pitched protodiastolic murmur simulating mitral diastolic rumble was recorded at the apex.

Hospital Course: Following admission, patient had moderate nocturnal paroxysmal dyspnea every night. He was treated with bed rest, low salt diet (NaCl 5 Gm. daily), digitalis (Digitoxin 0.15 mg. daily), chlorothiazide (0.5 to 1 Gm. daily), and aminophylline (250 mg. intravenously). There was significant response to the therapy and the patient became more comfortable. However, at the end of February, 1959, congestive heart failure became gradually manifest.

He complained of epigastric discomfort, anorexia and nausea. There was enlargement of liver, pretibial edema and a decrease in urine volume. At the beginning of April he had fever (102°F. to 104°F.) and hemoptysis. Ascites was also evident. He became progressively anemic and had hypoproteinemia (total serum protein 5.5 Gm./100ml.). In mid-May, he experienced episodes of acute pulmonary edema and severe pains over the right chest. On June 9, 1959, he died of congestive heart failure.

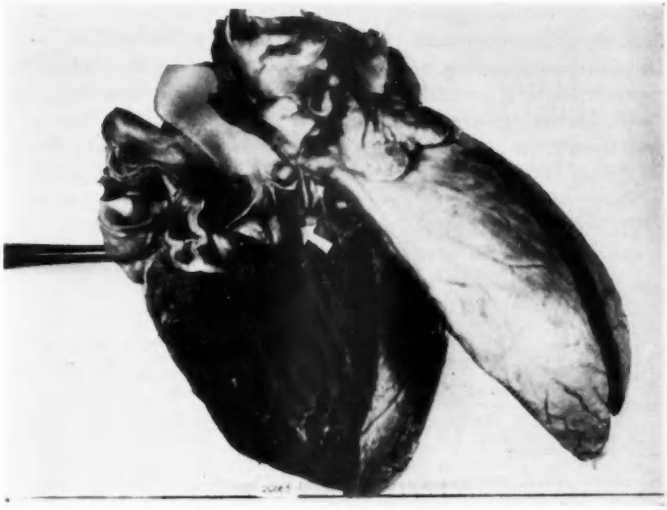


Fig. 4. Autopsy finding viewed from the left ventricular side.

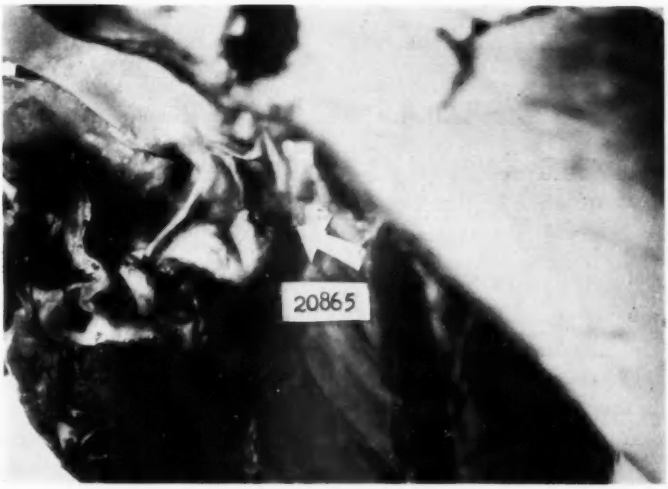


Fig. 5. Autopsy finding demonstrating the rupture of the aneurysm.

Autopsy: Pericardium revealed no abnormality. There were no pericardial adhesions. The heart weighed 580 Gm. and was greatly enlarged. The left ventricle was considerably and the right ventricle slightly hypertrophied. The right and left sinuses of Valsalva had undergone an aneurysmal enlargement, especially the former. The non-coronary sinus was normal. The aneurysm of the right coronary sinus ruptured into the left ventricle at the apex. The aortic valve was incompetent. The tricuspid, mitral and pulmonary valves were normal. Foramen ovale and ductus arteriosus were not patent. There was no septal defect. There was a thrombus in the right atrium. Histologic examination of wall of the sinus of Valsalva showed disappearances of elastic fibres, but it revealed no evidence suggesting a rheumatic or syphilitic endocarditis. At the aorta, there was no atheroma but mild mesoaortitis with a small aneurysm. There was a hemorrhagic pulmonary infarction with fibrinohemorrhagic pleurisy involving the middle lobe of the right lung. There were clear straw-colored pleural effusions. The right pleural cavity contained 1,200 ml. of fluid. At the left lower lobe, hypostatic pneumonia was observed. There were 400 ml. of clear yelloish ascites. The liver, spleen, kidneys and brain were congested. Marked peptic esophagitis was present and abscess of prostate and cystitis were also seen.

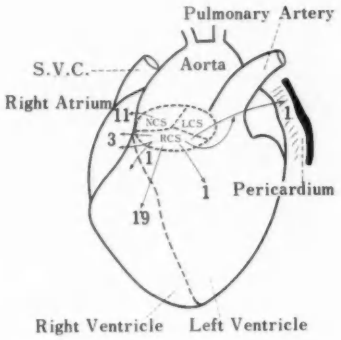
Discussion

Aneurysms of the sinuses of Valsalva were reviewed by Morgan Jones and Langley,[2] Oram and East,[3] Sawyers *et al.*[4] and Dubost and his associates.[5] It may be congenital or acquired. There is some difference of opinion as to the frequency of congenital aneurysm. Taussig[6] stated that these aneurysms were most commonly due to lues. However, Oram and East in a recent review of 23 aneurysms of the aortic sinus, described that 4 were syphilitic, 3 were bacterial and the rest were congenital in origin.

Aneurysms may originate in one or more of the sinuses of Valsalva. An aneurysm of the right coronary sinus is most frequently encountered. An aneurysm of the non-coronary sinus is second in frequency. Even rarer are aneurysms of the left coronary sinus of Valsalva.

Depending upon the anatomic location of the aneurysm, it extends into the interventricular septum or the wall of the ventricles or atriums. Aneurysms of the right coronary sinus rupture usually into the right ventricle, occasionally into the right atrium and rarely into the left ventricle or the pulmonary artery. Aneurysms of the non-coronary sinus tend to perforate into the right atrium. Aneurysms of the left coronary sinus perforate into the left ventricle or the pericardial sac.

Rupture of the aneurysm can occur at any time of life and is usually provoked by physical strains. The most common site of rupture is into the right ventricle and right atrium, and less commonly left ventricle, pericardial sac and pulmonary artery. These aneurysms occur more frequently in men than in women. As an unruptured congenital aneurysm is usually asymptomatic, we have difficulty in diagnosing it during life. Rupture is occasionally accompanied by severe precordial or substernal pain and shortness of



(SAWYERS, J. L. et al)

Fig. 6. Schema showing the incidences of the site of aneurysms and the site of their rupturing.

breath. The most frequent clinical picture of aneurysm of the sinus of Valsalva is that of aortic insufficiency due to dilatation of the aortic ring. The commonest cause of death after rupture is the congestive heart failure. Rarely, death may result from subacute bacterial endocarditis and cardiac arrhythmia or heart block as a result of a disturbance of the conductive system. Sudden death has been also reported at the time of rupture of aneurysm. Mean survival time after the rupture was 3.9 years by Sawyers.

The case reported here represents aneurysms of the right coronary sinus and the left coronary sinus of Valsalva. The former bulged into the left ventricle and ruptured into the left ventricular cavity. A definite clinical diagnosis was not established during life in this patient.

As no pathologic evidence of syphilis or subacute bacterial endocarditis was found, a congenital aneurysm with spontaneous rupture is postulated, although aortitis (etiology unknown) can not be absolutely excluded. After the review of the patient's clinical history, it seems probable that perforation occurred at the time, when the patient ran fast to get on a train on September 5, 1958. His death was no doubt the result of congestive heart failure with superimposed pulmonary infarction. Clinically, he represented the typical picture of aortic insufficiency.

Summary

A patient is described in whom an aneurysm of the right coronary sinus of Valsalva had ruptured into the left ventricle. This is believed to be the second report of such a case as far as we know.

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Combination of Ventricular Septal Defect and Aortic Insufficiency—Report of Two Cases

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COMBINATION of ventricular septal defect and aortic insufficiency is not frequent. Scott *et al.*[1] collected 22 cases with the autopsy findings from the previous reports and added seven probable cases, of which the diagnosis was confirmed by autopsy in two. Denton and Pappas[2] reported three other cases including one autopsy proven case. In Japan, one case of this combination with autopsy finding was presented by Sunata and his associates.[3]

Recently, we have made a clinical diagnosis of ventricular septal defect with aortic insufficiency on two patients and in both cases the diagnosis was confirmed by postmortem examination.

Case Report

Case 1. S.I., a 26-year-old male, was admitted to Tokyo University Hospital on December 19, 1958. The patient was known to have a heart murmur at one year of age. During his childhood he experienced frequent attacks of upper respiratory infection with occasional appearance of cyanosis. Thereafter he had had a fairly normal activity till June 1958, when he gradually developed malaise, dyspnea, palpitation and generalized edema.

On admission, physical examination revealed generalized edema but there was no cyanosis or clubbing of fingers. The blood pressure was 178/18–0 mm.Hg in the right arm and 130/40–0 mm.Hg in the left, the pulsation of the left radial artery being weaker than that of the right. The pulse was regular with the rate of 110, respiratory rate 30, and temperature 100°F.

The cardiac dullness was extended to the left and the apical impulse was palpable in the 6th intercostal space on the anterior axillary line. Auscultation of the heart revealed a harsh grade IV systolic murmur in the 4th and 5th intercostal spaces on the left sternal border transmitting to the apex. Over the base of the heart there was a systolic murmur of different character, which was followed by an accentuated second sound and a blowing loud diastolic murmur. Two diastolic extra sounds were heard at the apex. The phonocardiogram (Fig. 1) demonstrated a) a diamond shaped holosystolic murmur over the lower sternum, b) a decrescendo systolic murmur over the heart base, and c) crescendo-decrescendo diastolic murmur over the area between a) and b).

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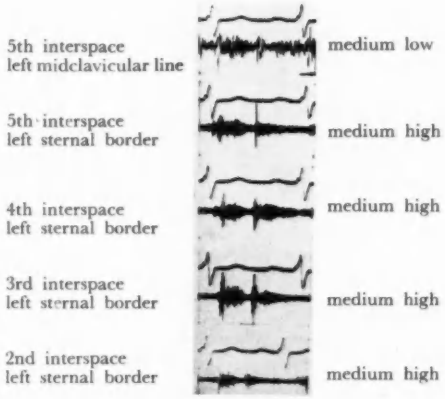

Fig. 1. Phonocardiogram of case 1.

Venous pressure was 180 mm. in water and circulation time was 55–85 sec. (arm to tongue). Serum reaction for syphilis was negative and a slightly abnormal liver function was detected by the liver function tests.

Chest X-ray (Fig. 2) demonstrated marked generalized cardiac enlargement

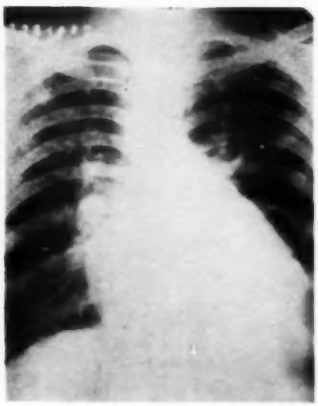

Fig. 2. Chest X-ray of case 1.

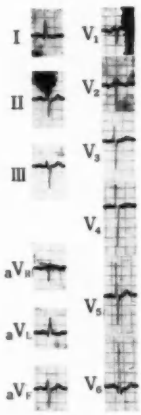

Fig. 3. Electrocardiogram of case 1.

and pulmonary vascular markings were increased. The aortic arch was small but was slightly prominent toward the right. The electrocardiogram (Fig. 3) showed left ventricular hypertrophy pattern with regular sinus rhythm.

A tentative diagnosis of ventricular septal defect with aortic insufficiency was made. The blowing diastolic murmur at the base of the heart was attributed to aortic insufficiency, the systolic murmur heard over the lower sternum and apex was considered to be due to ventricular septal defect, and the systolic murmur at the base was thought to be the ejection murmur caused by aortic insufficiency.

The extra sounds at the apex were proved to be the third heart sound and auricular sound by the phonocardiogram.

Complication of bacterial endocarditis was suspected because of persistent fever of about 100°F though several blood cultures were negative. The patient was treated with digitalis, diuretics and antibiotics but the signs of heart failure gradually progressed and he expired on January 24, 1959.

Fig. 4. Autopsy findings of case 1 viewed from the left ventricular side.

At autopsy, the heart weighed 760 Gm., showing marked left ventricular hypertrophy. A defect of 5 mm. in diameter was found in the membranous ventricular septum (Fig. 4). The aortic valves were involved by ulcerative verrucose endocarditis and there was aortic insufficiency caused by the destruction of the right aortic cusp. Besides these findings, a right aortic arch and an anomalous left subclavian artery were also noticed. The latter arose from a pulmonary vein but it was occluded at its origin and the blood was supplied through a branch of carotid artery.

Case 2.[4] H.M., a 27-year-old male, was admitted to Sensoji Hospital on December 6, 1958. The patient was known to have heart disease since the infancy. Since the age of 12 he had complained of palpitation and dyspnea on exertion and easy fatigability. Prior to the admission, these symptoms increased and resulted in a marked reduction of physical activity. At no time was there evidence of cyanosis or edema. The patient had had no history of rheumatic fever.

On physical examination, the blood pressure was 160/40–0 mm.Hg; pulse regular, rate 74; and respiratory rate 25. Serum reaction for syphilis was positive. The heart was enlarged to the left on percussion and the apical impulse was palpable on the anterior axillary line.

A grade III crescendo systolic murmur, which was relatively high-pitched, was heard in the 4th intercostal space on the left sternal border. In the 2nd left intercostal space, there was a harsh grade IV systolic murmur. Along the left sternal border, a blowing diastolic murmur was audible, which, together with the systolic murmur, produced a continuous murmur in the 3rd intercostal space.

Phonocardiogram (Fig. 5) revealed a) a crescendo holosystolic murmur in 4th left intercostal space, b) a systolic murmur with a distinctly different shape

in 2nd right intercostal space, and c) a decrescendo diastolic murmur in 3rd and 4th left intercostal space.

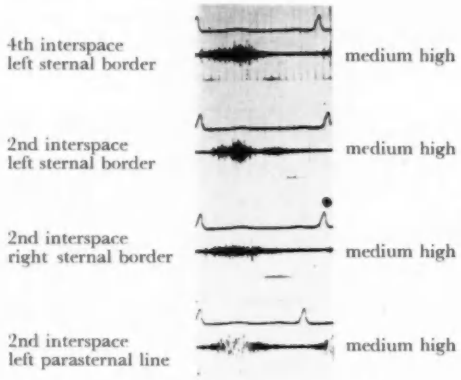

Fig. 5. Phonocardiogram of case 2.

Chest X-ray (Fig. 6) revealed moderate cardiac enlargement with slight prominence of the pulmonary artery. The electrocardiogram (Fig. 7) showed evidence of combined right and left ventricular hypertrophy with regular sinus rhythm.

On January 19, 1959, cardiac catheterization was performed at Tokyo University Hospital. The result (Table I) demonstrated a definite left to right shunt at the ventricular level, suggesting the existence of ventricular septal defect. Though a continuous murmur and a wide pulse pressure were recognized, no evidence of patent ductus arteriosus was found.

From the history, physical examination and the results of laboratory studies, including cardiac catheterization, the murmur a) was considered as an evidence of ventricular septal defect and c) as aortic insufficiency. The murmur b) was

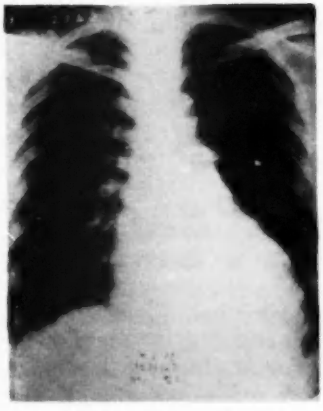

Fig. 6. Chest X-ray of case 2.

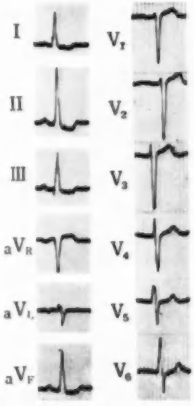

Fig. 7. Electrocardiogram of case 2.

Table I. Results of Cardiac Catheterization in Case 2.

Position	Pressure (mm.Hg)	O_2 content (vol. %)
Left pulmonary artery	15/5	13.2
Main pulmonary artery	20/5	13.9
Right ventricle (outflow)		13.6
Right ventricle (inflow)	22/0	11.6
Right auricle	5/−1	12.3
Inferior vena cava		9.3
Superior vena cava		12.2
Femoral artery	160/45	14.4

Arterial oxygen saturation: 96%
Oxygen consumption: 370 ml./min.

thought, as in case 1, to be the ejection murmur due to aortic insufficiency.

The patient was discharged from the Sensoji Hospital on February 10 with a maintenance therapy of digitalis (digitoxin 0.1 mg. per day). The patient was followed at out-patient clinic till February 16, 1959, when he died suddenly at his home.

At autopsy (Fig. 8), made at Tokyo University, the heart weighed 760 Gm., showing marked left ventricular hypertrophy and mild right ventricular hypertrophy. The aortic valve cusps were deformed by fibrous thickening. The

Fig. 8. Autopsy findings of case 2 viewed from the left ventricular side.

deformity was particularly marked in the right aortic cusp, which showed an aneurysmal dilatation toward the right ventricular chamber. Immediately below the right aortic cusp, a slit-like defect of the ventricular septum, 15 mm. in length, was found. No evidence of rheumatic, syphilitic or bacterial endocarditis was seen in aortic valves. Patent ductus arteriosus or other cardiovascular anomaly was not present.

Comment

Combination of ventricular septal defect and aortic insufficiency is uncommon. However, it is of particular importance for the therapy to differentiate this anomaly from similar conditions, especially from those of patent ductus arteriosus, an aneurysm of the sinus of Valsalva rupturing into the right ventricle or pulmonary artery, and an aortic septal defect.

From our own experiences and previous medical literatures, the following clinical features are considered to be useful for the correct diagnosis of this anomaly.

1) History: Usually, heart murmur is noted in the infancy or childhood. Generally, there is no episode of sudden occurrence of severe chest pain sometimes followed by rapidly progressing heart failure, which is encountered in some cases with rupture of an aneurysm of the sinus of Valsalva.

2) Auscultation and phonocardiogram: In most cases as described in previous reports, there are a loud systolic murmur in the left 2nd to 4th interspace and a blowing diastolic murmur along the left sternal border, producing a to-and-fro or continuous murmur, which is of little value for the differentiation from similar conditions mentioned above. In our cases, however, heart murmur could be divided into a) a systolic murmur due to ventricular septal defect, b) a diastolic murmur due to aortic insufficiency and c) an ejection murmur caused by aortic insufficiency. Each murmur could be distinguished by its character and maximal point in auscultation and by its shape in the phonocardiogram. This could be a considerable diagnostic help for the differentiation.

3) Other physical findings: Wide pulse pressure and low diastolic pressure are seen as the sign of aortic insufficiency. Cyanosis or clubbing is usually absent.

4) Chest X-ray: X-ray examination demonstrates prominent left ventricular enlargement, sometimes associated with slight enlargement of the right ventricle. The pulmonary artery segment is often prominent and the pulmonary vascular markings are increased because of increased pulmonary blood flow.

5) Electrocardiogram: The electrocardiogram usually shows left ventricular hypertrophy or combined right and left ventricular hypertrophy. In cases with ruptured aneurysm of the sinus of Valsalva, the electrocardiogram often shows right ventricular preponderance.

6) Cardiac catheterization: Cardiac catheterization reveals a left to right shunt at the ventricular level. There may be slight or moderate pulmonary hypertension. Arterial oxygen saturation is not lowered unless there is marked pulmonary hypertension. In cases with patent ductus arteriosus or aortic septal defect, the left to right shunt is detected at the level of pulmonary artery. If the catheter passes from the pulmonary artery into the aorta, the

existence of patent ductus arteriosus or aortic septal defect can be diagnosed with certainty.

7) Other laboratory studies: Selective angiocardiography with injection of contrast material into the left atrium or left ventricle may be valuable for the diagnosis of ventricular septal defect when the shunt is small and can not be elicited by cardiac catheterization. Thoracic aortography may serve to confirm or exclude the presence of a patent ductus, aortic septal defect or ruptured aneurysm of the sinus of Valsalva.

Summary

(1) Two cases of ventricular septal defect with aortic insufficiency were presented.

(2) The diagnosis was confirmed at autopsy in both cases. In one case, an associated right aortic arch and anomalous left subclavian artery were also noticed.

(3) Differentiation of this lesion from similar conditions, especially those of the patent ductus arteriosus, ruptured aneurysm of the sinus of Valsalva and aortic septal defect, was discussed.

(Case 2 was published in "Naika" 4:385, 1959 in Japanese).

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Massive Occlusion of the Main Pulmonary Artery and Its Primary Branches with Subsequent Cor Pulmonale—A Case Report

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Yamato MISHINA, M.D., Hiroya SAHEKI, M.D.,
and Kiyoshi MACHII, M.D.

THE incidence of massive occlusion of the main pulmonary artery and its primary branches is quite low.[1)-5)]

Keating[6)] made a brief review of the literature during the period from 1908 to 1951 about the chronic pulmonary obstruction. Carroll[7)] reported 5 cases of the massive obstruction of the major pulmonary arteries in 1950. Ring[3)] described 21 cases of chronic massive pulmonary artery thrombosis from a total of 11,511 consecutive autopsies, giving an incidence of 0.18 per cent. Magidson[8)] reported 7 cases of thrombosis of major pulmonary arteries as cause of death from 35,003 autopsies, with an incidence of only 0.02 per cent. Ball[1)] described a total of 23 cases, 9 of which were seen in life, while the remaining 14 were obtained from an examination of 7,000 autopsy records.

Moreover, a report with a long survival after the initial episode is quite rare.[1)6)]

In this report, we emphasize the prolonged survival of our patient.

Case Report

H.F., a 37-year-old man was admitted to the Tokyo University Hospital in August, 1957, complaining of progressive shortness of breath on exertion, general weakness and palpitation.

In November, 1945, he suffered from hemoptysis, dyspnea on exertion, palpitation and cough, and became aware of edema and varices in lower extremities. These symptoms and signs increased their severity gradually but steadily in next 10 years. During these years many studies were made to exclude the possibility of a pulmonary tuberculosis.

In April, 1957, there was a gross edema of the abdominal wall and both legs with dilatation of superficial veins and an enlargement of liver. At this time he was told that he had some heart disease.

On admission, physical examination revealed a man with dyspnea but no cyanosis. Blood pressure was 124/72 mm.Hg, pulse was regular and the rate of 110 per minute. The heart was enlarged and the 2nd heart sound in the pulmonary area was markedly split and a faint pulmonary systolic murmur was noted.

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There was an enlargement of liver.

Laboratory studies revealed no polycythemia or anemia.

The values of bleeding time, coagulation time and prothrombin time were within normal limits.

Venous pressure was 105 mm. in water.

X-ray studies: The chest X-ray taken in September, 1952, revealed that the lung fields were clear and cardiac shadow was within normal limit in contour and size (Fig. 1). However, on admission in August, 1957, prominence of the

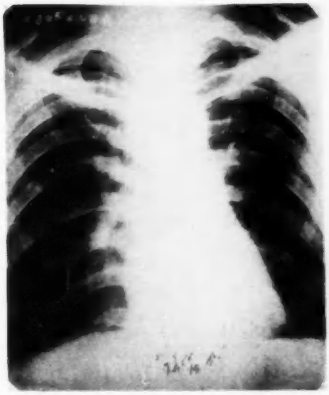

Fig. 1. Heart shadow and lung fields are normal (November, 1952).

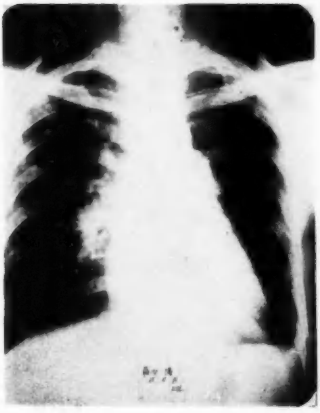

Fig. 2. Prominence of the pulmonary artery, cardiac enlargement, and clear lung field on the left side (August, 1957).

pulmonary arteries was noted. Left lung field was more radiolucent than the right, and it seemed likely that the occlusion of the left primary branch of the pulmonary artery might have already been present at this time (Fig. 2).

The electrocardiogram indicated right ventricular hypertrophy and incomplete

right bundle branch block (Fig. 3).

The phonocardiogram showed the splitting of the 2nd heart sound and a faint

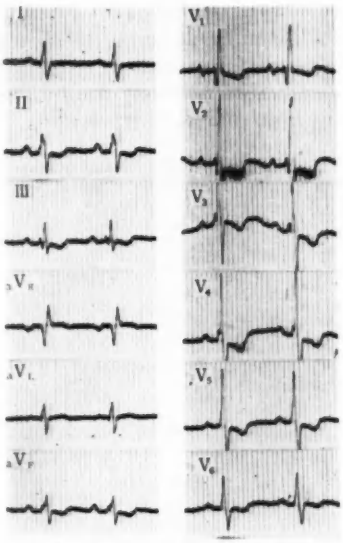

Fig. 3. Right ventricular hypertrophy and incomplete right bundle branch block are seen in the electrocardiogram.

systolic murmur (Fig. 4).

Pulmonary function tests revealed vital capacity to be 3,120 ml. (81.5% of the predicted value). Maximal breathing capacity was 70 L./min. (68.6% of the predicted value). Residual volume to total lung capacity ratio was normal (28%). Arterial oxygen saturation was slightly reduced (91.4%).

Serologic test for syphilis gave negative result.

On admission, cardiac catheterization was attempted, but insertion of the catheter was impossible because of the thrombus in the great saphenous vein and the femoral vein.

During the hospitalization, he responded moderately well to the treatment, and his condition remained relatively stationary. At this time another chest X-ray was taken which showed an enlarged heart with congestion in the right lung field (Fig. 5). On December 15, 1957, the patient had an attack of sudden dyspnea on exertion and lapsed into coma. He died the following day.

Autopsy findings: The significant pathological finding was a huge thrombotic pulmonary embolus which straddled the bifurcation of the main pulmonary artery and its primary branches bilaterally (Fig. 6). The left primary branch was occluded completely. Recanalization of the old thrombus was seen in the intrapulmonary branch of the pulmonary artery (Fig. 7). The old thrombi were found in the pulmonary arterioles (Fig. 8). In the main pulmonary artery there were reactive proliferation of the intima and rupture of elastic fiber of the media (Fig. 9). Many small infarcts and thrombi were present in both lungs. In the right lower lobe, a fresh

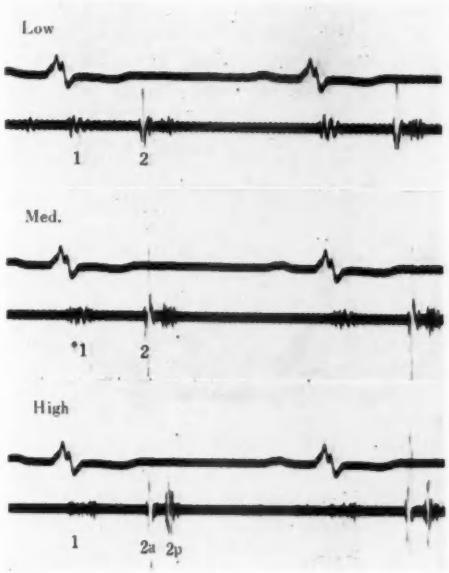

Fig. 4. The phonocardiogram in the second intercostal space. The second heart sound is markedly split. The pulmonary component is not accentuated. Systolic murmur is faint.

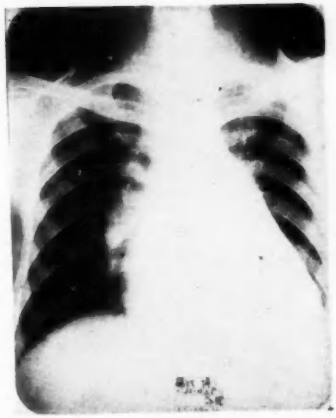

Fig. 5. Progressive cardiac enlargement and prominence of the pulmonary artery (December, 1957).

infarct was found, which was considered to be the direct cause of death. The old thrombi with recanalization were present in the left pulmonary branch (Fig. 10) as well as the inferior vena cava and the common iliac vein (Fig. 11). The right ventricular wall averaged 6 mm. in thickness and the left 10 mm. The

Fig. 6. Opened right ventricle with thrombotic mass locating just above the pulmonic valve. The left pulmonary artery is completely occluded.

Fig. 7. Longitudinal section of intrapulmonary portion of the left pulmonary artery showing the recanalization.

right ventricle was moderately hypertrophied. The aorta was normal.

The schema of the main pathological findings was shown in Fig. 12.

Discussion

It has been often considered that thrombosis in the pulmonary arterial tree is always secondary to an embolism.

Hollister[2] described that the major cause of this syndrome was attributed to an embolism rather than a complication of pulmonary arteriosclerosis, chronic pulmonary disease or mitral stenosis. Ring[3] had the same opinion, and he divided this syndrome as follows:

Fig. 8. The old and recent thrombi in the pulmonary arterioles of the right lung.

Fig. 9. The main pulmonary arterial wall. Reactive proliferations of the intima are seen and elastic fibers of the media are partially disappeared.

Fig. 10. Cross section of the left pulmonary artery presenting the recanalization.

(1) those imposed upon a previous embolus.
(2) those arising in situ without any previous embolic episode.

Brenner[9] and Ball[5] reported the primary thrombus in the pulmonary artery and Irvin[10] reported another case due to a congenital anomaly of the pulmonary artery.

The factors that are considered to predispose the thrombus formation in situ are diffuse pulmonary disease, pulmonary hypertension, dehydration, anoxemia and altered coagulability of the blood. In our case, it is considered

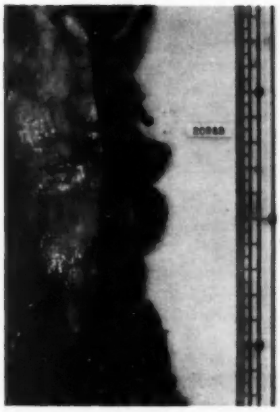

Fig. 11. The old thrombosis of the inferior vena cava and the common iliac vein with recanalization. The aorta (left side) is normal.

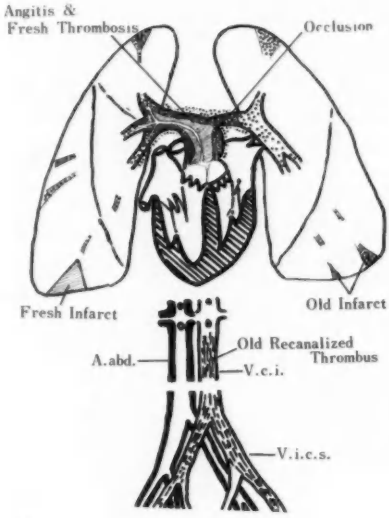

Fig. 12. Schema of the main pathologic findings.

that the presence of leg vein thrombosis predisposed the occurrence of pulmonary embolism and the spread of secondary thrombus upon an embolus.[8]

Side of obstruction: Ring[3] described the predominance of right sided thrombus and pointed out that even in case of bilateral thrombosis the obstruction began from the right side. Savaccol[11] explained it by the fact that the pulmonary artery was "squeezed" between the vein and bronchus on the right side, while it was free on the left. However, in our case, complete

occlusion was found on the left side.

Symptoms and signs: The clinical picture of pulmonary thrombosis is often masked by underlying and complicating lesions of the heart and lungs.

The symptoms are in general those of right heart failure and low cardiac output. Symptoms including dyspnea, hemoptysis, cough, chest or epigastric pain, mental confusion, cyanosis, peripheral edema, hepatic engorgement and elevated jugular venous pressure are important.

X-ray findings: The main pulmonary artery is enlarged, and the lung fields appear radiolucent when cardiac failure is absent.

The electrocardiogram: Hypertrophy of the right ventricle has been reported in some cases.

Murmurs are not characteristic.[1] Ball[5] described that the pulmonary systolic murmur and splitting of the 2nd sound might suggest the obstruction.[4]

Why Our Patient Had a Long Survival?—

The pulmonary circulation has a great reserve, a ready distensibility of the smaller vessels and a large number of reserve capillaries. Furthermore, there is a considerable collateral circulation between the pulmonary and bronchial arterial branches.[3] Bloomer *et al.* showed a "great and rapid rise in the amount of blood circulating through the bronchial artery in the dog after the ligation of the pulmonary artery." Experimentally, it was confirmed that death did not occur until roughly 90 per cent occlusion of the main pulmonary artery was produced in dogs.[13] Probably, our case had a great reserve of the pulmonary circulation. The collateral circulation was unrecognized.

Summary

A case of massive occlusion of the main pulmonary artery and its branches was reported. A case of this type is quite rare because of the long duration of the process from the initial episode.

The pulmonary artery occlusion in this case was considered to be derived from the leg vein thrombosis.

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